Visual mismatch negativity (vMMN): A review and meta-analysis of studies in psychiatric and neurological disorders

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Abstract: The visual mismatch negativity (vMMN) response is an event-related potential (ERP) component, which is automatically elicited by events that violate predictions based on prior events. VMMN experiments use visual stimulus repetition to induce predictions, and vMMN is obtained by subtracting the response to rare unpredicted stimuli from those to frequent stimuli. One increasingly popular interpretation of the mismatch response postulates that vMMN, similar to its auditory counterpart (aMMN), represents a prediction error response generated by cortical mechanisms forming probabilistic representations of sensory signals. Here we discuss the physiological and theoretical basis of vMMN and review thirty-three studies from the emerging field of its clinical applications, presenting a meta-analysis of findings in schizophrenia, mood disorders, substance abuse, neurodegenerative disorders, developmental disorders, deafness, panic disorder and hypertension. Furthermore, we include reports on aging and maturation as they bear upon many clinically relevant conditions. Surveying the literature we found that vMMN is altered in several clinical populations which is in line with aMMN findings. An important potential advantage of vMMN however is that it allows the investigation of deficits in predictive processing in cognitive domains which rely primarily on visual information; a principal sensory modality and thus of vital importance in environmental information processing and response, and a modality which arguably may be more sensitive to some pathological changes. However, due to the relative infancy of research in vMMN compared to aMMN in clinical populations its potential for clinical application is not yet fully appreciated. The aim of this review and meta-analysis therefore is to present, in a detailed systematic manner, the findings from clinically-based vMMN studies, to discuss their potential impact and application, to raise awareness of this measure and to improve our understanding of disease upon fundamental aspects of visual information processing.

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Visual mismatch negativity (vMMN): A review and meta-analysis of studies in psychiatric and neurological disorders

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ABSTRACT

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clinical populations which is in line with aMMN findings. An important potential advantage of vMMN however is that it allows the investigation of deficits in predictive processing in cognitive domains which rely primarily on visual information; a principal sensory modality and thus of vital importance in environmental information processing and response, and a modality which arguably may be more sensitive to some pathological changes. However, due to the relative infancy of research in vMMN compared to aMMN in clinical populations its potential for clinical application is not yet fully appreciated. The aim of this review and meta-analysis therefore is to present, in a detailed systematic manner, the findings from clinically-based vMMN studies, to discuss their potential impact and application, to raise awareness of this measure and to improve our understanding of disease upon fundamental aspects of visual information processing.

1. Introduction

Mismatch negativity (MMN) studies often use passive oddball paradigms, where unattended stimuli are repeated to induce an automatic prediction pertaining to the probability of an event. This prediction is often thought about as 'regularity' extracted from the stimulus stream (Winkler, 2007) and its presence is usually demonstrated indirectly by showing that stimuli that deviate from the frequent stimuli evoke a mismatch response (e.g., Stefanics, Csukly, Komlosi, Czobor, & Czigler, 2012; Stefanics, Kimura, & Czigler, 2011; Stefanics, Kremláček, & Czigler, 2014). MMN studies thus investigate the effect of stimulus repetition by focusing on neural responses specific to rare (deviant) events embedded in a stream of frequent (standard) stimuli. The emphasis in many MMN studies therefore falls on automatic change detection, which is crucial for survival as unexpected environmental changes may carry important information that might trigger an orientation reaction (Sokolov, 1963). Nevertheless, this is only possible if probabilities of environmental events are continuously monitored and updated.

The MMN component, originally described in the auditory domain (aMMN) (Näätänen, Gaillard, & Mantysalo, 1978), has its analogs in the other sensory modalities as well and has been systematically explored in the visual domain for more than twenty years (for the first review, see Pazo-Alvarez, Cadaveira, & Amenedo, 2003, for more recent reviews, see Kimura, Schröger, & Czigler, 2011; Stefanics et al., 2014). At the time of writing this article in January 2016, PubMed (www.pubmed.com) returned **100** entries for the term *"visual mismatch negativity (vMMN)"*. Similar to auditory MMN, that can be elicited by unexpected changes in different stimulus features, such as pitch, duration, intensity, etc. (for a review, see Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010), there is evidence that visual MMN can be elicited by rare changes in features such as line orientation (Astikainen, Lillstarng, & Ruusvirta, 2008; Astikainen, Ruusuvirta, Wikgen, & Korjonen, 2004; Czigler & Pató, 2009; Czigler & Sulykos, 2010; Flynn, Liasis, Gardner, Boyd, & Towell, 2009; Kimura, Katayama, Ohira, & Schröger, 2009; Kimura, Widmann, & Schröger, 2010), spatial frequency (Heslenfeld, 2003; Kenemans, Jong, & Verbaten, 2003; Kenemans, Hebly, van den Heuvel, & Grent-'T-Jong, 2010; Maekawa et al., 2005; Sulykos & Czigler, 2011), color (Czigler, Balázs, & Pató, 2004; Czigler, Balazs, & Winkler, 2002; Grimm, Bendixen, Deouell, & Schröger, 2009; Horimoto, Inagaki, Yano, Sata, & Kaga, 2002; Kimura, Katayama, & Murohashi, 2006; Liu & Shi, 2008; Mazza, Turatto, & Sarlo, 2005; Mo, Xu, Kay, & Tan, 2011; Müller et al., 2010; Stefanics, Kimura, et al., 2011; Thierry, Athanasopoulos, Wiggett, Dering, & Kuipers, 2009), luminance (Stagg, Hindley, Tales, & Butler, 2004), illusory brightness (Sulykos & Czigler, 2014), or motion (Amenedo, Pazo-Alvarez, & Cadaveira, 2007; Kremláček et al., 2006; Kuldkepp, Kreegipuu, Raidvee, Näätänen, & Allik, 2013; Lorenzo-López, Amenedo, Pazo-Alvarez, & Cadaveira, 2004). Furthermore, again similar to aMMN that can be elicited by rare changes in more abstract attributes of the acoustic stimuli than simple physical features, vMMN is also sensitive to higher-level attributes such as sequential regularities (Stefanics, Kimura, et al., 2011), object structure (Müller, Widmann, & Schröger, 2013), symmetry (Kecskés-Kovács, Sulykos, & Czigler, 2013a), laterality of body parts (Stefanics & Czigler, 2012), or attributes of socially more relevant stimuli such as facial emotions (Astikainen & Hietanen, 2009; Fujimura & Okanoya, 2013; Stefanics et al., 2012; Susac, Ilmoniemi, Pihko, Ranken, & Supek, 2010; Susac, Ilmoniemi, Pihko, & Supek, 2004; Zhao & Li, 2006), as well as facial gender (Kecskés-Kovács, Sulykos, & Czigler, 2013b). Thus, there is ample evidence that automatic perceptual predictive mechanisms operate in the visual modality too, which can be probed by experimentally manipulating statistical properties of a wide variety of stimulus attributes or their relationships.

Early accounts of the aMMN suggested that MMN generation relied on a strong auditory sensory memory trace encoding the repeating stimulus (Winkler, 2007). More recent theories suggest that the perceptual system extracts environmental regularities and represents expected events; i.e., the formation of predictions has been suggested as the primary function of the neural processes underlying the MMN (Winkler & Czigler, 1998). The basis of both auditory and visual MMN studies is the ubiquitous phenomenon that brain response properties to frequent events differ from those to rare events. Specifically, repeated events elicit an attenuated response, a phenomenon often referred to outside the MMN

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field as repetition suppression (RS), stimulus-specific adaptation (SSA), or neural priming (e.g., Desimone, 1996; Grill-Spector, Henson, & Martin, 2006). RS is widely considered a manifestation of an active memory representation, established by the previous stimulation, that might also depend on the experience of the subjects with the given stimulus category (Grotheer & Kovács, 2014; Sulykos, Kecskés-Kovács, & Czigler, 2015), i.e., perceptual expertise. Often referred to as 'functional magnetic resonance imaging adaptation' (fMRIa), the method is particularly popular in neuroimaging to explore functional properties of neuronal populations (Krekelberg, Boynton, & van Wezel, 2006). While studies on RS or SSA investigate response attenuation over repetitions, MMN studies focus on the relative difference between suppressed and unsuppressed brain responses to predicted and unpredicted stimuli, respectively. Adaptation research and the MMN field thus focus on effects of manipulation of stimulus probabilities from different angles, although they use similar experimental techniques to study closely related phenomena.

Stimulus repetition often results in faster reaction times (RTs) or improvement in stimulus detection and RS of the hemodynamic response has been associated with behavioral phenomenon of priming (Buckner, Koutstaal, Schacter, & Rosen, 2000; Henson & Rugg, 2003; Schacter & Buckner, 1998; Wig, Grafton, Demos, & Kelley, 2005; Wiggs & Martin, 1998). Adaptation studies in psychophysics tend to use continuous stimulus exposure instead of stimulus repetition to study perceptual and behavioral effects. From the perspective of predictive coding longer exposure and stimulus repetition both provide the visual system with more sensory evidence about the probable external cause of the perceived stimulus. Psychophysics defines visual adaptation in terms of brief or long exposures and the ensuing aftereffects (Webster, 2011). Thus, in psychophysics the term adaptation is used to describe perceptual changes that follow exposure to recently viewed stimuli. Adaptation is primarily characterized by a loss in sensitivity to the adapting stimulus which is accompanied by a boost in neural responses to unexpected events. At the behavioral level adaptation can facilitate discrimination (e.g., Kristjansson, 2011; McDermott, Malkoc, Mulligan, & Webster, 2010) similar to priming paradigms, and unexpected stimuli that are associated with MMN are also detected more easily (Garrido, Sahani, & Dolan, 2013; Solomon & Kohn, 2014; Tiitinen, May, Reinikainen, & Näätänen, 1994).

In electrophysiology simpler forms of use-dependent adaptation of firing rates are distinguished from more sophisticated, context-dependent SSA (Kohn, 2007; Nelken, 2014; Pérez-González & Malmierca, 2014). Using the term 'adaptation' to describe stimulus-specific attenuation of neural activity in electrophysiology is somewhat unfortunate (Nelken & Ulanovsky, 2007). According to a widely accepted definition by Dudai (2002), adaptation is a "Use-dependent response decrement that occurs because of sensory and peripheral processes". SSA is not use-dependent, that is, the reduction in the response to a stimulus does not generalize, or only partially generalizes, to other, rare stimuli (Movshon & Lennie, 1979; Nelken, 2014). A better term for SSA would be "habituation", defined by Dudai (2002) as the "gradual diminution of the response to a stimulus following the repeated presentation of the same, or a similar, stimulus". Habituation shows stimulus-specificity, rate-sensitivity, and other characteristics of SSA. The nomenclature is problematic (Nelken & Ulanovsky, 2007), and without looking at the details of the phenomena in question, one might easily get confused and/or swamped in semantics. Since different fields use the terms RS, SSA, habituation, adaptation or refractoriness to describe several related but distinct concepts and phenomena, it is difficult to pin one concept on one term (O'Shea 2015; Stefanics, Kremláček, & Czigler, 2016).

SSA is a complex phenomenon, most probably representing a compound of distinct neuronal processes. The exact mechanisms and neurophysiological effects of SSA in the visual system are not fully understood yet (Grill-Spector et al., 2006; Ibbotson, 2005; Solomon & Kohn, 2014). Nevertheless, at least three mechanisms have been identified, including 1) somatic afterhyperpolarization, 2) synaptic depression due to the depletion of vesicles from the presynaptic terminal, and 3) synaptic (network) mechanisms (Kohn, 2007). Since the 'refractory' state of a neuron after spiking is too short to be responsible for the ERP amplitude decrease after repeated stimulation and synaptic depletion also occurs presumably only at higher stimulation rates than in MMN experiments, RS in MMN experiments likely results from network mechanisms. The proposed mechanisms involve increased inhibition or decreased excitation (Ibbotson, 2005). Adaptation effects are substantially more complex than suggested by traditional fatigue-based descriptions which focused on mechanisms in individual cells. Our emerging understanding is that adaptation modifies neural population coordination and its effects cascade through the processing stages, affecting networks further down the processing stream (Solomon & Kohn, 2014).

Several attempts have been made to identify the single-cell correlates of the scalp-recorded aMMN. SSA is the closest known single-neuron phenomenon of aMMN (for reviews see Escera and Malmierca, 2014; Nelken, 2014; Nelken and Ulanovsky, 2007; Pérez-González & Malmierca, 2014). The magnitudes of SSA and aMMN are both negatively correlated with the probability of the deviant but positively correlated with the difference between standard and deviant. However, an important difference is the earlier timing of SSA relative to aMMN, therefore Nelken and Ulanovsky (2007) suggested that SSA is a correlate of change detection in the primary auditory cortex upstream of MMN. This is in line with a recent EEG study where SSA was found to depend critically on statistical context in the auditory cortex (Herrmann, Henry, Fromboluti, McAuley, & Obleser, 2015), and that aMMN itself is a compound response of primary and higher-level cortical areas with longer response latencies. Adaptation has been observed in electrophysiological studies throughout the visual system including the retina (Hosoya, Baccus, & Meister, 2005), thalamus (Solomon, Peirce, Dhruv, & Lennie, 2004), superior colliculus (Boehnke et al., 2011), and several cortical areas (Kaliukhovich & Vogels, 2014; Kremláček et al., 2007; Meyer, Ramachandran, & Olson, 2014; Motter, 2006; Müller, Metha, Krauskopf, & Lennie, 1999; Ramachandran, Meyer, & Olson, 2016; for a review, see Vogels, in press). Although the exact relationship of adaptation at different levels of the visual processing hierarchy to change detection as observed in vMMN studies (e.g., Kimura et al., 2011; Stefanics et al., 2014) is

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not clear, there is general agreement that the function of adaptation is to match response properties of the sensory system to the current environment (Clifford et al., 2007; Webster, 2011) and thus improve stimulus discrimination or detection of improbable stimuli (Benucci, Saleem & Carandini, 2013; Carandini & Heeger, 2012; Kohn, 2007; Solomon & Kohn, 2014; Wark, Lundstrom, & Fairhall, 2007).

Three models of network mechanisms have been put forward (Grill-Spector et al., 2006) to explain RS in terms of population dynamics. The model of *neural fatigue* is similar to the idea of "refractoriness" in the MMN field, and explains RS by firing rate attenuation, i.e., where the initial high neural response rate of spiking to a constant stimulus is not maintained but instead declines over time; a common feature of many sensory neurons (Hille,1992; Pérez-González & Malmierca, 2014). The second model proposes that RS involves *sharpening* of the neural populations that generate the initial response, such that fewer neurons respond to repeated stimuli (Henson & Rugg, 2003; Wiggs & Martin, 1998). Specifically, neurons responding to features that are not essential for recognizing the object attenuate their responses, thus the network becomes sparser and more selective (Wiggs & Martin, 1998), thus according to this view, RS is a by-product of sharpening stimulus representations in the cortex (Desimone, 1996; Kok, Jehee, & de Lange, 2012). The third model explains RS effects by *facilitation* of stimulus processing, based on faster accumulation of evidence necessary for recognition (James & Gauthier, 2006). The accumulation model proposes that stimulus information is accrued faster following repetition thus activity returns to baseline faster, which in turn, might result in the decreased cumulative hemodynamic response (Grill-Spector et al., 2006; James et al., 2006).

The facilitation model shows a strong similarity to a more recent adaptation-based model of the MMN, which proposed that the MMN is generated by fresh-afferent activity of cortical neurons, the latency and amplitude of which is modulated during stimulus repetition (May & Tiitinen, 2010). However, other recent studies using neurobiologically informed computational models (Garagnani & Pulvermüller, 2011; Wacongne, Changeux, & Dehaene, 2012) found that the MMN is likely to be generated by active cortical predictive mechanisms rather than passive adaptation. The dynamics of the network that is thought to generate the aMMN has been extensively investigated with large-scale models which incorporate hypotheses of both adaptation and change detection (Garrido et al., 2008; Garrido, Kilner, Kiebel, Stephan, & Friston, 2007; Garrido, Kilner, Stephan, & Friston, 2009; Kiebel, Garrido, & Friston, 2007). Results of these dynamic causal modeling (DCM) studies show that RS is associated with repetition-dependent plasticity in connections within and between generating structures suggesting a conjoint role of adaptation (May & Tiitinen, 2010) and active model-adjustment (Winkler, Karmos, & Näätänen, 1996) processes in the aMMN response. The potential of predictive coding theory to provide a comprehensive explanation of MMN phenomenology is demonstrated by a recent modeling study which suggest that the aMMN reflects approximate Bayesian learning of sensory regularities (Lieder et al., 2013a), where prediction errors (i.e., aMMN responses) are used to adjusts a probabilistic model of the environment (Lieder et al., 2013b). Assuming that vMMN has a functionally similar role in the visual system to that of aMMN in the auditory system, the implication of these modeling studies is that visual perception is an active process relying on an internal probabilistic representation of the world (cf. Wolfe, 1999) which serves to predict the incoming sensory signal and vMMN is a neural correlate of the update process when there is a mismatch between the predicted and incoming signal.

The predictive coding theory elegantly accommodates adaptation effects observed in psychophysics, behavioral priming, RS, as well as ERP components including the MMN (Friston, 2005). Predictive coding posits that the brain actively generates probabilistic models of the causes of the sensory input (for a comprehensive review, see Clark, 2013), and provides a framework which explains both response attenuation to repeated events and a larger response to unpredicted events. Predictive coding emphasizes the active nature of perceptual inference: instead of being a passive analyzer of bottom-up sensory information (Egner, Monti, & Summerfield, 2010), the brain is thought to actively predict the sensory signal by generating a probabilistic model of the causes of the sensory signals. Thus, according the theory, perception is actively using a set of probabilistic assumptions to infer the most likely cause of the sensory signals by matching incoming sensory information to prediction of that signal (Friston, 2005; Lee & Mumford, 2003; Rao & Ballard, 1999). Repetition effects are thought to reflect ongoing statistical learning during which the generative model is updated. In MMN studies RS often manifests as decrease of the negative component elicited by rare events, i.e., as a relative positivity to repeated stimuli, which was suggested to represent rapid SSA underlying sensory memory formation (Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). Predictive coding suggests that RS is brought about by fast changes in synaptic connections (Baldeweg, 2006, 2007; Garrido et al., 2009) within and between hierarchical levels of neural populations. Top-down predictions based on prior events are thought to explain away prediction errors at lower hierarchical levels, thus RS effects have been proposed to reflect fulfilled perceptual expectations (Summerfield, Trittschuh, Monti, Mesulam, & Egner, 2008; but cf. Grotheer & Kovács, 2015). On the other hand, MMN responses are increasingly considered as automatic bottom-up prediction error signals (Friston, 2005, 2010; Stefanics, Kimura, et al., 2011; Stefanics et al., 2014; Winkler, 2007), the neural correlates of updating of generative models of the environment by plastic changes in synaptic weights after the violation of the model's prediction by an unexpected event, i.e., a deviant stimulus. These generative models can be viewed as hierarchical representations of observed events of the environment, similar to predictive perceptual object representations suggested by Winkler and Czigler (2012).

While RS is a tool used relatively seldom in clinical research, the aMMN has a long track record in studying clinical populations. Besides its important contribution to the understanding of automatic sensory processing, the aMMN is a promising technique for clinical research and possibly also for clinical applications, as it might help to better understand disease mechanisms and dissect spectrum diseases into well-defined subgroups to guide diagnosis, predict disease

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trajectory and response to treatments (Light & Näätänen, 2013; Luck et al., 2011). Recording the aMMN is a non-invasive and cost-effective method, and in the case of patients with limited cooperation, it allows assessment of brain function without using a behavioral task. The applications of aMMN as a clinical research tool have been extensively reviewed (Näätänen & Kähkönen, 2009; Näätänen et al., 2011, 2012a; Näätänen, Paavilainen, Rinne, & Alho, 2007; Näätänen, Sussman, Salisbury, & Shafer, 2014). However, the literature is still lacking a comprehensive review of vMMN studies with clinical relevance. Among articles concerning vMMN, we found **33** studies describing its use in a clinical context, and in the following we review these articles and compare their findings to those obtained in aMMN studies. In particular, we summarize the findings in schizophrenia, mood disorders, substance abuse, neurodegenerative disorders, developmental disorders, deafness, panic disorder and hypertension and present a meta-analysis of the reviewed studies in the Discussion section. Furthermore, we include reports on aging and maturation as these processes impact on several clinically relevant conditions.

2. Visual MMN studies in clinical populations

In general, visual MMN has been used to study similar neuropsychiatric and neurological disorders as the auditory MMN. We list studies in Table 1 for each disorder that we overview in the following sections.

2.1. *Schizophrenia*

Schizophrenia is a chronic psychotic disease with diverse and severe symptoms which limits cognitive, affective and social functioning. The disorder is primarily characterized by so-called positive symptoms like delusions, hallucinations and thought disturbances, and negative symptoms such as blunted emotions, social withdrawal, catatonic behavior and lack of spontaneity. Furthermore, cognitive impairments are widely considered to lie at the core of the illness (Buchanan et al., 2005) and include symptoms of deficits in attention, memory, and executive functions (Barch & Ceaser, 2012; Heinrichs & Zakzanis, 1998). Prevalence of schizophrenia is 0.6 % in the general population (McGrath, Saha, Chant, & Welham, 2008), it requires long-term treatment and is associated with a decreased life expectancy. In spite of the advances in neurobiological research (structural, functional or genetic) the pathophysiology of this heterogeneous disease is not fully understood. For over 40 years of research on the neurobiology of schizophrenia, dopamine dysregulation emerged as one of the most robust findings, which is currently attributed to elevated dopamine synthesis capacity in the disease (Fusar-Poli & Meyer-Lindenberg, 2013).[1] However, the dopamine dysregulation hypothesis does not explain cognitive deficits and negative symptoms. The current view, beside a dysregulation of the dopaminergic system, also incorporates misbalanced glutamatergic and GABAergic (Gamma-aminobutyric acid) neurotransmitters (Marsman et al., 2013)[2] mediating cortical processing (pyramidal cells/interneurons) and supporting the notion of aberrant sensory processing (Lee et al., 2012; Lewis, 2014). In fact, interactions of glutamatergic NMDAR (N-Methyl-D-Aspartate receptor) and dopamine receptors are a key mechanism in multiple pathophysiological theories of schizophrenia (Frohlich & Van Horn, 2014).

NMDARs play a key role in synaptic transmission and in the synaptic plasticity underlying fundamental cognitive functions such as learning and memory (Zorumski & Izumi, 2012) and it has been hypothesized that modulation of plasticity underlying predictive representations is abnormal in schizophrenia (Javitt, 2004; Moghaddam & Javitt, 2012; Stephan, Baldeweg, & Friston, 2006; Stephan, Friston, & Frith, 2009). Beyond predictive processes, there is now much evidence for a general hypofunction of NMDARs in schizophrenia (Coyle, 2012; Heekeren et al., 2008; Javitt, 2012; Stahl, 2007; Umbricht & Krljes, 2005). Despite much research over the past decades, we still lack sensitive and non-invasive laboratory tests in psychiatry that predict whether an at-risk individual will transition to psychosis. There is a general consensus (Luck et al., 2011) that new biomarkers providing reliable and sensitive measures of neuro-cognitive functioning could be used to predict clinical course in prodromal individuals before the onset of psychosis. Thus, ideally, early intervention would become possible. Furthermore, such biomarkers would dramatically facilitate the development of treatments for cognitive dysfunction in mental illnesses.

One of the promising candidate ERP components is the aMMN (Näätänen et al., 2011a, 2011b) which has emerged as one of the most reliable electrophysiological alterations in meta-analyses of schizophrenia (Umbricht & Krljes, 2005). More recent research has focused on the corresponding paradigm in the visual domain using the visual MMN (Csukly, Stefanics, Komlósi, Czigler, & Czobor, 2013; Farkas, Stefanics, Marosi, & Csukly, 2015; Urban, Kremláček, Masopust, & Libiger, 2008). According to an increasingly popular interpretation, the auditory and visual MMN represent a prediction error response generated by cortical mechanisms forming probabilistic representations of sensory signals (Friston, 2010; Stefanics & Czigler, 2012; Stefanics et al., 2014). MMN deficits are one of the features in schizophrenia that indicate severe abnormalities in fundamental brain processes of prediction and inference (Corlett et al., 2007; Friston, Stephan, Montague, & Dolan, 2014; Stephan et al., 2006). This is further corroborated by parallel evidence for a key role of NMDAR in MMN generation and in the pathophysiology of schizophrenia (Coyle, 2006; Javitt, 2009; Umbricht & Krljes, 2005).

[1] Support for the dopamine hypothesis is mostly based on an effect of dopamine receptor antagonists in treatment of positive schizophrenia syndromes – i.e., delusions, hallucinations, disorganized speech/behavior, and on an observation that drugs increasing dopamine (amphetamines, levodopa) levels induced psychotic symptoms in healthy volunteers.

[2] The main support for the glutamate hypothesis comes from experiments with ketamine, NMDAR antagonist widely used in subanesthetic doses as pharmacological model of schizophrenia due to its psychomimetic properties (Corlett et al., 2011; Kocsis et al., 2013; Pomarol-Clotet et al., 2006).

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Table 1 – vMMN clinical studies according to clinical topics. Q3

Source/Diagnosis/ number in figures	Group	vMMN Stimuli	Results	Intergroup vMMN differences		Correlation between vMMN and (clinical) parameters
				Temporal interval (effect size, power)	Area/Electrode	
Schizophrenia and schizoaffective disorder						
(Csukly et al., 2013) Schizophrenia 1	Patients 24 evaluated, 4 excluded (11F, 34.2 ± 10.3 y), ASEm CG 24	Emotional faces (happy, fearful)	NO significant vMM response for patients	170–220 msec^{PD} (*eCd = 0.87, Pw = 0.84*) 250–360 msec^{PD} (*eCd = 0.74, Pw = 0.71*)	Temporal left ROI (happy); central ROI (happy)^{PH}; (6 ROIs) (128) Temporal right ROI (fearful); central ROI (happy)^{PH}; (6 ROIs) (128)	YES: more positive vMM response in happy condition (central ROI) correlated positively to overall emotion recognition similarly for patients and CG; vMM response changed polarity;
(Farkas et al., 2015) 2	Patients 28 (12 F, ϕ 37.7 ± 8.4 y) CG 27 (12 F, ϕ 38.2 ± 10.6 y)	Shape: horizontal and vertical high frequency grating	Smaller vMM in patients	90–200 msec^{PD} (*eCd = 0.76, Pw = 0.79*)	Bilateral and sagital occipito-parietal ROIs (negativity vMMN) and right and sagital prefrontal ROIs^{PD}; (6 ROIs) (128)	NO: no correlation to age, illness duration, PANSS scores, antipsychotic doses, Personal and Social Performance
(Neuhaus et al., 2013) Schizophrenia 3	Patients 22 (10F, ϕ 40.67 ± 11.3 y), CG 24 (11F, ϕ 37.96 ± 7.3 y)	Shape: X or O	Smaller vMMN in patients	250–350 msec, ^{PD} (*eCd = 1.05, Pw = 0.93*)	Bilateral inferior temporo-occipital areas^{PD}; (2 ROIs) (64)	NO: but before correction for multiple comp. larger vMMN was related to better GAF score
(Urban et al., 2008) Schizophrenia 4	Patients 24 (5F, 27.90 ± 9.25 y), ASm CG	Motion direction: periphery of visual field	Smaller vMMN in patients	100–200 msec^{PH} (*eCd = 0.76, Pw = 0.73*)	Oz, O2, Pz, Fz^{PH} (6)	YES: smaller vMMN was related to deficit syndrome score (Fz) and daily dose of antipsychotics (Fz, Cz)
Mood disorders						
(Y. Chang et al., 2010) Major depressive disorder 5	exp. 1 Patients 15 (9F, ϕ 40.3 ± 11.2 y), Am CG 15 exp. 2 patients 10 (7F, ϕ 44.0 ± 15.8 y), ASm CG 10	Faces: schematic – neutral: standard; happy, and sad: deviants	Smaller or absent vMMN for patients; no modulation by inverted face position in depression;	120–200 msec^{PD} (*eCd = 0.97, Pw = 0.73 for exp. 1*) 220–320 msec^{PD} (*eCd = 1.20, Pw = 0.89 for exp. 1*)	TP7/TP8, M1/M2, P7/P8, O1/O2^{PD}; (32) TP7/TP8, M1/M2, P7/P8, O1/O2^{PD}; (32)	not assessed
(Y. Chang et al., 2011) Major depressive disorder 6	Patients 14 medication-free (5F, 41.4 ± 12.6 y), ASm CG	Shape: 1 or 2 bars	NO reduction in the oddball-vMMN (deviant-standard); decreased deviant-control response for patients	150–250 msec^{PD} (*eCd = 1.06, Pw = 0.77*) 250–320 msec^{PD} (*eCd = 0.87, Pw = 0.60*)	T5/T6, O1/O2^{PD}; (32) T5/T6, O1/O2^{PD}; (32)	YES: smaller late-vMMN was related to higher depression scores but not with anxiety or MMSE
(Maekawa et al., 2013) Bipolar disorder 7	Patients 20 (10F, 40.8 ± 11.0 y), A SEm CG 20	Shape: windmill patterns of different spatial frequency	Smaller and less lateralized vMMN response for patients	200–350 msec^{PD} (*eCd = 2.05, Pw = 1.00*)	Right temporo-occipital area^{PD}; (128)	YES: smaller vMMN at Oz was related to higher lithium dosage (mood stabilizer)
(Qiu et al., 2011) Major Depressive Disorder 8	Patients 20 (12F, ϕ 41.6 ± 13.0, 23–62 y), ASm CG 20	Duration: presentation time of squares	Smaller vMMN amplitude to long duration deviants in patients, NO difference for short deviants	200–250 msec^{PD} (*eCd = 0.71, Pw = 0.59*)	O1, O2, Oz^{PD}; (32)	NO: no correlation to depression severity

Substance abuse						
(Fisher et al., 2010) Nicotine 9	Non-smokers 27 (7F, ϕ 22.14 ± 0.79 y), each under nicotine/ placebo condition	Shape: bars	Larger vMMN for nicotine in O1 and O2	Whole interval (up to 900 msec) (*eCd = 0.82, Pw = 0.84*)	O1, $O2^{PD}$ (15)	Not assessed
(He et al., 2014) Alcohol 10	Healthy social drinkers 12 (2F, 22.75, 21–25 y) under alcohol and placebo condition	Color, location and duration: two circular patches	Alcohol reduced vMMN amplitude for location and duration deviants, not for color deviant	150–230 $msec^{PD}$ (location) (*eCd = 1.08, Pw = 0.43*) 150–280 $msec^{PD}$ (duration) (*eCd = 0.94, Pw = 0.34*)	Left parietal-occipital electrode cluster (P1, P3, P5, PO3, PO5) and the right parietal-occipital electrode cluster (P2, P4, P6, PO4, $PO6)^{PD}$ (64)	Not assessed
(Hosák et al., 2008) Methamphetamine abuse 11	Patients 17 (3F, ϕ 24.4 ± 4.4 y) ASm CG 17	Motion direction: periphery of visual field	Abuse duration dependency: vMMN was higher for short term abusers and lower for long term abusers	120–240 $msec^{PD}$ (*eCd = 0.86, Pw = 0.68*)	Pz (6)	YES: vMMN was smaller with increase of abuse duration (O_L, O_R, Oz, Pz) or age (Oz, Pz)
(Kenemans et al., 2010) Alcohol 12	16 subjects (8F, ϕ 21.7 ± 2.0 y) under alcohol and placebo condition	Spatial frequency of gratings	vMMN reduction for alcohol compared to placebo condition (3 subjects excluded)	150–170 $msec^{PD}$ (*eCd = 0.98, Pw = 0.36*)	Oz^{PD} (62)	NO: vMMN unrelated to post-experiment blood alcohol concentration
Neurodegenerative disorders (Alzheimer disease, SCA, and mild cognitive impairment)						
(Iijima et al., 1995)[a] Dementia of various etiologies 13	Young 20 (20–29 y) elder 20 (60–79 y) patients 18 (58–78 y)	Shape: X or O	NO differences in vMMN among groups	No difference (*eCd Pw NA*)	No difference in Fz, Cz, Pz^{PD} (3)	NO: no correlation to MMSE
(Kremláček et al., 2011) SCA type 2 14	Patients 10 (5F, 25 –72 y) CG 54 (16 F, 19 –57 y)	Motion direction: periphery of visual field	NO pathological vMMN	100–200 $msec^{PD}$ (*eCd Pw NA*)	Oz^{PD} (6)	YES: vMMN (Oz) get smaller or more positive with age or SCA onset (related) and negatively to CAG repeats – contra intuitive dependence
(Tales & Butler, 2006) AD 15	Probable AD 8 (8F, ϕ 73; 52–84 y) aged controls 12 (10F, ϕ 73.2; 51–84 y) young controls 11 (8F, ϕ 28; 20–43 y)	Shape: 1 or 2 bars	NO differences in vMMN among AD and aged control groups vMMN absent in first 16 trials for patients, larger in amplitude for last 16 trials in the block (as compared to healthy elder)	250–400 $msec^{PD}$ (*eCd = 1.93, Pw = 0.98*)	T5, T6, O1, $O2^{PD}$ (13)	Not assessed
(Tales et al., 2008) AD, MCI 16	Probable AD 10 (8F, ϕ 75.2; 67–81 y) amnestic MCI 8 (2F, ϕ 74.5; 65–82 y) Am CG 10 (6F, ϕ 71.2; 65 –81 y)	Shape: 1 or 2 bars	Early vMMN larger for patients (similar for AD and MCI, second half of testing – not tested for the intergroup difference)	140–250 $msec^{PD}$ (*eCd Pw NA*)	T5, T6, O1, O2, Oz, Pz^{PD} (14)	Not assessed

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Table 1 – (*continued*)

Source/Diagnosis/ number in figures	Group	vMMN Stimuli	Results	Intergroup vMMN differences		Correlation between vMMN and (clinical) parameters
				Temporal interval (effect size, power)	Area/Electrode	
(Stothart et al., 2014) AD, amnesic MCI 17	AD patients 20 (13F, ϕ 79.2; 60–91 y) amnesic MCI patients 25 (9F, ϕ 77.3; 62–91 y) controls 26 (12F, ϕ 76.0; 62–88 y)	Shape: 1 or 2 bars	Smaller vMMN (or even positivity) in aMCI compared to controls NO differences in vMMN between AD and controls	147–213 msec^{PH} (AD) 146–234 msec^{PH} (old, aMCI) *(eCd = 0.91, Pw = 0.89)*	Occipital ROI^{PD} (averaged O1, Oz, O2, PO9, PO10, PO7, PO8) (64)	YES: smaller vMMN was related to lower MMSE
Developmental disorders (autism, dyslexia, mental retardation)						
(Cléry, Bonnet-Brilhault, et al., 2013) ASD 18	Patients 12 (2F, 11.6 ± 1.8, 8–14 y) ASm CG	Shape, motion: circle deformation	Earlier vMM in patients, In CG occipito-parieto-temporal negativity around 330 msec and positivities around 280 and 450 msec, in ASD several positivities in 50–300 msec followed by a occipito-parietal positivity around 400 msec	300–410 msec^{PH} *(eCd Pw NA)* 400–600^{PH} *(eCd Pw NA)* 500–600 msec^{PH} *(eCd Pw NA)*	Occipito-parieto-temporal sites^{PH} (29) T4^{PH} (29) T4, C4, CO2, M2, Iz, T6^{PH} (29)	not assessed
(Cléry, Roux, et al., 2013) ASD 19	Patients 13 (2F, 26.2 ± 5.0 y) CG 13 (5F, 24.3 ± 2.0 y)	Shape, motion: circle deformation	NO vMMN in ASD, late positivity instead	180–240 msec^{PH} (negativity in CG) *(eCd Pw NA)* 210–250 msec^{PH} (negativity in CG) *(eCd Pw NA)* 350–600 msec^{PH} (positivity in AD) *(eCd Pw NA)*	Occipito-parietal electrodes^{PH} (29) Fronto-central sites^{PH} (29) occipito-temporo-parietal sites^{PH} (29)	Not assessed
(Gayle et al., 2012) Autism Spectrum Quotient in controls 20	CG 45 (16 F, 19.8 ± 1.7 y)	Faces: happy and sad compared to neutral	Not assessed	150–425 msec^{PD} *(eCd = 0.73, Pw = 0.52)*	Parieto-occipital electrodes (PO3,PO4, PO7, PO8)^{PD} (72)	YES: higher Adult Autism Spectrum Quotient score was related to a smaller vMMN in PO8 for happy faces
(Horimoto et al., 2002) Children with mental retardation 21	Patients 10 (5F, ϕ 11.2; 9–15 y) Am CG 12 (5F, ϕ 10.0; 7–13 y) adult CG 11 (9F, ϕ 28.5 y)	Color: blue, red or greenish blue square	Different distribution of vMMN	160–400 msec^{PH} *(eCd Pw NA)*	Pz, Oz in control children, Pz, Cz in patients^{PH} (4)	Not assessed
(Maekawa et al., 2011) High-functioning ASD 22	Patients 11 (3F, ϕ 28, 18–40 y) CG 11 (7F, ϕ 28,9, 20–38 y)	Shape: windmill patterns of different spatial frequency	NO differences in vMMN between groups	150–350 msec^{PD} *(eCd Pw NA)*	Oz^{PD} (128)	Not assessed

(Wang et al., 2010) Developmental Dyslexia (DD) 23	Patients 11 (4F, ϕ 10.8 ± 0.8 y) age matched CG 12 (6F, ϕ 10.5 ± 0.5 y) Reading-level matched CG 13 (9F, ϕ 9.2 ± 0.3 y)	Motion direction: low contrast, low spatial frequency (magnocellular) or high contrast, high spatial frequency (control)	Smaller vMMN for DD as compared to both control groups NO difference for control motion between groups	150–250 msec^{PH} (magnocellular motion) *(eCd = 1.15, Pw = 0.77)* 200–300 msec^{PH} (control motion) *(eCd Pw NA)*	Oz^{PD} (32) Oz^{PD} (32)	Not assessed
Aging/Maturation						
(Cleary et al., 2013) Maturation 24	Children 22 (13F, ϕ 10.4 ± 1.43, 8–12 y), 21 in the final analysis Adults 20 (10F, ϕ 26.6 ± 5.65, 18–42 y)	Pattern: spatial frequency of horizontal gratings	Lower vMMN amplitude in children Higher positive amplitude in children	Around 150 msec *(eCd = 0.72, Pw = 0.61)* Around 250 msec *(eCd = 0.70, Pw = 0.59)*	O1, O2^{PH} (O1, O2, F3, F4 out of 13) F3, F4^{PH} (O1, O2, F3, F4 out of 13)	Not assessed
(Cléry et al., 2012) Maturation 25	Children 12 (2F, ϕ 11.3 ± 1.6; 8–14 y) adult controls 12 (5F, ϕ 24 ± 2.2; 20–30 y)	Shape, motion: circle deformation	vMMN with three peaks (150–350 msec, posteriorly) and later positivity in children, in adults occipito-parietal negativity (180–240 msec) followed by fronto-central negativity (210–250 msec)^{PH}	130–160 msec^{PH} (more negativity in children) 250–310 msec^{PH} (more positivity in children) 350–400 msec 400–600 msec	Temporo-parietal sites^{PH} (29) Fronto-central sites^{PH} (29) FC1, FT3,FC2, FT4, C3, T3, TP3^{PH} (29) C4, T4, CP2, TP4, P4, T5^{PH} (29)	Not assessed
(Horimoto et al., 2002) Maturation 26	Control children 12 (5F, ϕ 10.0; 7–13 y) Adult controls 11 (9F, ϕ 28.5 y)	Color: blue, red or greenish blue square	More often 2 peaks in children, early peak with larger amplitude in children	180–400 msec^{PH} *(eCd Pw NA)*	Fz, Cz, Pz, Oz^{PD} (4)	Not assessed
(Tanaka et al., 2001) Maturation 27	Newborns 83 (35–43 weeks of conceptional age, incl 11 potentially with cognitive dysfunction), vMMN recorded from 63	depth/shape: Ramachandran patterns (convex/concave)	vMMN latency shortened during maturation	Latency decreased from 519 msec to 418 msec between 35 and 37 week of conceptional age *(eCd = 2.15, Pw = 0.83)*	Pz^{PD} (4)	YES: vMMN latency shortened with conceptional age from 35 to 37 week
(Tomio et al., 2012) Maturation 28	107 normal subjects (52 F, 2–27 y)	Depth/shape: Ramachandran patterns (convex/concave)	vMMN latency shortened during maturation	Latency decreased from 2–3 y (394 ± 58 msec) untill 16 y (273 ± 32 msec) *(eCd = 2.73, Pw = 0.99)* stable (275 ± 44 msec) for age >18 y	Pz^{PD} (4)	YES: vMMN latency shortened with age
(Iijima et al., 1996) Aging 29	Elders 20 (12F, 60–9 y) young 20 (11F, 20–29 y)	Shape: X or O	NO vMMN difference (peak, latency); later N2b difference in latency considered as attention related;	NO difference in 70–250 msec^{PH}	No difference in Fz, Cz, Pz^{PD} (3)	Not assessed

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Table 1 – (*continued*)

Source/Diagnosis/ number in figures	Group	vMMN Stimuli	Results	Intergroup vMMN differences		Correlation between vMMN and (clinical) parameters
				Temporal interval (effect size, power)	Area/Electrode	
(Lorenzo-López et al., 2004) Aging 30	Elders 9 (5F, ϕ 62.0 ± 3.0, 58–67 y) Middle-aged 5 (2F, ϕ 49.0 ± 4.0, 45–54 y) young 7 (4F, ϕ 32.0 ± 6.0, 24–38 y)	Motion direction: up or down	Smaller average amplitude with age Smaller amplitude in older group	165–205 msec^{PH} (*eCd = 0.94, Pw = 0.41*) 145–165 msec^{PH}	Regardless of age maximal at occipital and temporal sites (20) No vMMN in O1, Oz, T5, P3^{PH} in older group (8 posterior electrodes)	Not assessed
(Stothart et al., 2013) Aging 31	Elders 17 (8F, ϕ 76.8 ± 6.1, 66–86 y) Young 17 (10F, ϕ 20.8 ± 3.1, 18–31 y)	shape: 1 or 2 bars	NO vMMN amplitude or duration difference	138–264 msec (*eCd = 0.17, Pw = 0.08*)	No vMMN differences in occipital ROI (7 posterior electrodes from 64)	not assessed
(Tales et al., 2002) Aging 32	Elders 12 (8F, ϕ 77, 69–88 y) Young 24 (16F, ϕ 30.5 y)	shape: 1 or 2 bars	smaller average amplitude in elders	250–400 msec^{PD} (*eCd = 0.97, Pw = 0.81*)	T5, T6, O1, Oz, O2^{PH} (14)	not assessed
(Tales & Butler, 2006) Aging 33	Aged controls 12 (10F, ϕ 73.2; 51–84 y) Young controls 11 (8F, ϕ 28; 20–43 y)	Shape: 1 or 2 bars	Smaller average amplitude in elders	250–400 (*eCd = 1.18, Pw = 0.77*)	T5, T6, O1, O2^{PD} (13)	Not assessed
Miscellaneous						
(Bottari et al., 2014) Deafness 33	Patients 12 (7F, 35.9 ± 3.0 y) Controls 12 (6F, 31.6 ± 2.2 y)	Shape, motion: circle deformation	Smaller amplitude for patients in posterior and larger in central area	153–292 msec^{PH} (*eCd = 1.93, Pw = 0.99*)	left-right x frontal, central, posterior clusters^{PD} (34)	Not assessed
(Si et al., 2014) Hypertension 34	Patients 15 (7F, 55.3 ± 7.5 y) ASEm CG	Duration: onset of squares rectangles in periphery	vMMN smaller in patients vMMN delayed in patients	cca150–300 msec$^{PD, PH}$ (*eCd = 0.90, Pw = 0.66*) 216 msec for CG and 240.8 msec for patients (*eCd = 0.90, Pw = 0.66*)	TP7, A1, A2, O1, Oz^{PH} (main effect for 7 PD electrodes out of 32) temporal-occipital regions, O1^{PH} (main-effect for 7 PD electrodes out of 32)	NO: vMMN unrelated to MMSE and blood pressure
(Tang et al., 2013) Panic disorder 35	Patients 12 (8F, 47.8 ± 10.7 y) Controls 17 (11F, 39.4 ± 14.7 y) comparable in ASE and handedness	Faces: schematic-positive, negative, neutral	vMMN smaller for positive/ negative emotions in patients	220–330 msec$^{PD, PH}$ (*eCd = 0.92, Pw = 0.67*)	TP7/TP8 and O1/O2^{PH} (also M1/M2 and T5/T6 contributed to main-effect, altogether 32 electrodes)	NO: no correlation between vMMN amplitudes and the panic, anxiety or depression scales

Q14

Notes: *AD* – Alzheimer disease, Am – age matched, *ASD* – Autism Spectrum Disorder, ASE – age, sex, education, respectively, ASEm – age, sex, education matched, ASm – age and sex matched, *CAG* – cytosine–adenine–guanine, CG – control group, *DD* – developmental dyslexia, eCd – equivalent Cohen's *d* (see the *Effect size and power of the vMMN studies*), *MCI* – Mild Cognitive impairment, *MMSE*-Mini-Mental State Examination, *NA* – not available, *PD* – pre-determined interval or electrodes where vMMN difference was looked at, total number of electrodes used in parentheses, *PH* – post-hoc difference in interval or electrodes, *Pw* – study power, *SCA2* – spinocerebellar ataxia type 2, *vMM* – visual mismatch.

[a] Only abstract is available.

Although vision *per se* is not predominantly deteriorated in schizophrenia, numerous visual deficits have been identified, such as deficits in lateral inhibition, smooth eye movements, motion detection, contrast sensitivity, and recognition of faces and facial-expressions (Butler, Silverstein, & Dakin, 2008; Yoon, Sheremata, Rokem, & Silver, 2013). Furthermore, visual hallucinations are present in about 27% of schizophrenia patients (Waters et al., 2014). Magnetic resonance spectroscopy showed that increased levels of glutamine and decreased levels of glutamate in schizophrenic patients were not restricted to the frontal regions, but were evident also in the occipital lobe (Chang et al., 2007; Keshavan et al., 2009). Structural changes in the primary visual cortex have been found post-mortem (Dorph-Petersen et al., 2009). The relationship between the glutamate dysregulation and vision was confirmed in a human study administering the NMDA-receptor inhibitor ketamine. During ketamine infusion, subjects had a decreased aMMN amplitude and also impaired processing of visual context (Umbricht et al., 2000).

In the first vMMN report in schizophrenia, Urban et al. (2008) used motion-onset stimuli in the visual periphery while subjects attended to a motion-detection task in the central visual field. The authors reported a smaller vMMN to changes in motion direction in patients with schizophrenia (for details see Table 1) than in age- and gender-matched controls. The cumulative vMMN amplitude at the 100–200 msec interval was smaller in the occipital, parietal and frontal derivations than that of controls. The vMMN deficit was observed only in patients with deficit symptoms (assessed by Schedule for the Deficit Syndrome), a finding which corresponds to the glutamatergic hypothesis and early sensory deficit. However, further analyses showed that there was an association of the vMMN impairment with a higher dose of medication, a lower global assessment of functioning (GAF) score or the duration of the illness. Furthermore, there were no differences between patients with illness duration shorter than 3 years and controls. These findings support the view of the motion-onset vMMN as a state marker of schizophrenia.

In a recent study Farkas et al. (2015) used rare changes in the orientation of Gabor patches to elicit vMMN in a group of patients with schizophrenia, and in age- and education-matched controls. Controls had significant vMMN in the occipito-temporal region and showed a positive deviance detection activity (vMMP) in prefrontal region, both within an interval 90–200 msec after stimuli onset. In contrast to the control group, patients did not exhibit significant vMMN or vMMP and showed a lower absolute response amplitude in parieto-occipital and prefrontal areas (Fig. 1). The authors did not find any relationship between patient's deviance detection activity and age, illness duration, equivalent dose medication, and their functional status. While the impairment of an early deviance processing resembles results reported by Urban et al. (2008), the absence of any relationship to the clinical markers does not. The reason of such discrepancy may lay in different patient groups. Patients in Urban's group had a lower medication dose (Urban 366 ± 257 *vs* Farkas 731 ± 322 in clp. equivalents mg/day), were younger (27.9 ± 9.25 *vs* 37.7 ± 8.4 years), and with a shorter illness duration (7.1 ± 10.04 *vs* 11.7 ± 7.23 years).

Beside changes in low-level visual paradigms, more complex natural stimuli such as facial expressions have been used in order to assess automatic change detection in schizophrenia (Csukly et al., 2013). The authors compared a group of patients with age-, gender- and education-matched controls. Four different faces were simultaneously displayed in the visual periphery showing either fearful or happy expressions. To minimize attentional effects in the processing of the face stimuli participants engaged in a centrally presented task which involved detection of changes in the orientation of a fixation cross. VMMN elicited by changes in facial emotions was observed in two time intervals, at 170–220 msec and 250–360 msec post-stimulus, over occipital, right temporal and central scalp regions. Patients had a significantly smaller vMMN in the left temporal area in the earlier interval for the happy deviant faces and in the right temporal area in the later interval for the fearful deviant faces. The groups showed different responses also in the central area for the happy deviant faces in both intervals, however, the mismatch activity ("deviant − standard") observed here was positive and larger in controls. The authors found no correlation between the mismatch response and medication or symptoms severity, which supports the view that the impairment in the automatic change detection of peripherally presented emotional expressions might be a trait rather than state marker. A significant correlation was found between the activity in the central electrode sites for the happy deviant faces and emotion recognition performance.

In another recent study, Neuhaus, Brandt, Goldberg, Bates, and Malhotra (2013) reported that amplitude of the differential response was smaller in the schizophrenia group than in controls at the latency of 250–300 msec in inferior occipito-temporal regions. However, this study used a paradigm where participants were attending the stimuli, and they were instructed to indicate the "deviant" stimulus by a button press. Thus the stimuli eliciting the MMN were also task-relevant, which renders interpretation of the results ambiguous, as differential activity observed in this study might be related to predictive processes, attention, or executive processes (for the role of attention in the vMMN generation, see Czigler, 2007; Stefanics et al., 2014).

Summary of vMMN studies in schizophrenia

While there are only four vMMN studies yet in patients with schizophrenia, their results unanimously point to impaired predictive processes in vision. This is well in line with deficits in auditory MMN which have been widely explored for more than three decades, and since the first report of an aMMN deficit (Shelley et al., 1991), there have been **256** articles published addressing this issue (source PubMed, *"MMN" schizophrenia*, May 2015). Most of these studies showed an aMMN amplitude reduction in schizophrenia (Todd, Michie, Schall, Ward, & Catts, 2012; Umbricht & Krljes, 2005) and, moreover, this sensory deficit was associated with the impaired daily functioning of the patients (Todd, Harms, Schall, & Michie, 2013). The aMMN sensitivity to the sensory deficit depends on the type of deviance used, e.g., pitch, intensity, or duration, with the duration violation being the most sensitive test as shown by a meta-analysis of 32 reports (Umbricht & Krljes, 2005). Correlations between aMMN and clinical measures

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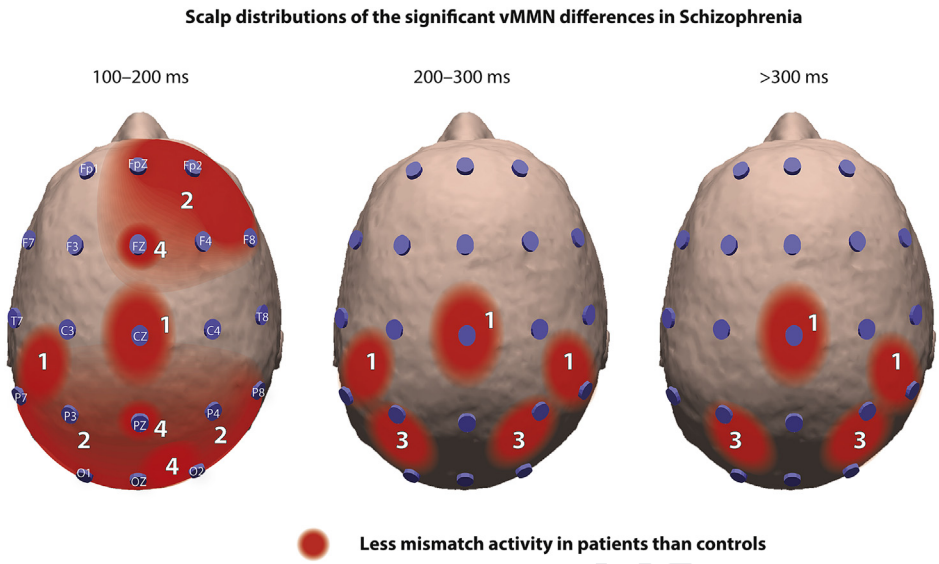

Fig. 1 – Scalp areas of a significant amplitude difference in the deviance-related activity between schizophrenic patients and controls. Numbers represent the following studies according to Table 1: 1 – Csukly et al. (2013), 2 – Farkas et al. (2015), 3 – Neuhaus et al. (2013), and 4 – Urban et al. (2008). Highlighted areas represent ERP effects as measures on the scalp. About the limited correspondence between scalp potential maps and cortical sources, see the Technical notes section at the end of the paper.

have been mostly weak when prodromal population and patients with the first hospitalization criteria or patients' healthy relatives have been studied (Todd et al., 2013). Generally, the numerous reports on aMMN elicited by duration or pitch deviance show a consistent picture, whereas vMMN findings are mosaic-like, since in the visual domain there have only been a few studies, each using a specific design.

The NMDAR hypofunction hypothesis is perhaps the most powerful model of schizophrenia, with a strong translational potential. Currently the aMMN component is widely used as a proxy for NMDAR deficits in schizophrenia. Although we still lack experimental evidence that deficits in visual MMN are mediated by NMDAR hypofunction similarly to aMMN deficits, there is compelling evidence that vMMN is also impaired in schizophrenia. Direct comparison between the aMMN and vMMN in schizophrenia is thus warranted. Future studies should investigate heterogeneity in schizophrenia and consider dividing patients into subgroups along behavioral, genetic or molecular endophenotypes as well as variability in vMMN. Using experimental paradigms with appropriate control for attention and stimulus probability effects (Stefanics et al., 2014) will help reduce variability among studies due to confounding variables. In summary, exploration of vMMN as a research tool, or as a potential biomarker in schizophrenia is highly justified.

2.2. *Mood disorders*

Major depression disorder (MDD) is one of the most common forms of psychopathology. It affects approximately one in six men and one in four women at least once during their lifetimes (Kessler, 2012; Kessler et al., 2003), and its 12-month prevalence is approximately 5.5 % (Bromet et al., 2011). The most frequent symptoms in MDD include depressed mood, sleeping problems, fatigue and suicidal thoughts or intentions, whereas bipolar disorder (BP), another diagnosis with disturbance in mood, is characterized by recurring depressive and manic periods (American Psychiatric Association, 2013). Both theoretical (Beck, 1967, 1976) and empirical (Mineka & Sutton, 1992) work suggests that a cognitive bias is an important feature of mood disorders. According to Beck's cognitive theory of depression (1967, 1976), dysfunctional attitudes, negative schemata, and faulty information processing are critical factors that predispose individuals to experience episodes of depression. The neural mechanisms underlying disturbances in cognitive functions are poorly understood, and they may be present even at the level of automatic information processing (for a review, see Beck, 2008). Therefore several studies used aMMN (or its magnetic counterpart, MMNm) to study automatic sensory-cognitive processes in depression (Iv, Zhao, Gong, Chen, & Miao, 2010; Kähkönen et al., 2007; Lepistö et al., 2004; Pang et al., 2014; Takei et al., 2009) and BP (Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Takei et al., 2010).

Takei et al. applied magnetoencephalography to measure information processing deficit in depression (2009) and BP (2010). In the study of depressive patients, MMNm was elicited in response to duration and frequency changes of pure-tone stimuli and in response to an across-category change in a vowel. The magnetic global field power (mGFP) of the MMNm was significantly smaller in the group of depressive disorder patients than in the healthy control group. Kähkönen et al. (2007) found that the aMMN amplitude in the EEG (but not its magnetic counterpart) was increased in depression compared to controls. It is not clear why both amplitude increase and decrease of MMN have been found related to depression. One possibility is that the contradictory results can be explained by differences in stimulus conditions or patient populations.

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When patients with BP were studied using an aMMN paradigm, no amplitude differences were found, but mGFP of MMNm in the right hemisphere for pure-tones was delayed in patients with BP compared to healthy participants (Takei et al., 2010). In addition, the MMNm dipole in the left hemisphere was located inferiorly in patients with BP compared to that in healthy group.

Alterations of MMN did not correlate with clinical symptoms in either of the patients groups. The lack of correlation between aMMN (Kähkönen et al., 2007; Pang et al., 2014; Takei et al., 2009) and depression symptoms suggests that sensory-cognitive deficit in depression is a trait-not a state-dependent phenomenon.

Regarding potential alterations of elementary sensory visual feature processing in mood disorders, three studies tested the modulation of the vMMN to low-level visual features. Chang et al. (2011) exposed depressive and control participants with pictures of double white bars ("deviants") interspersed with single white bars ("standards") drawn on a black background. The participants attended to changes in the color of a square in the fixation point. The vMMN was compared between the groups at two latency ranges: 150–250 msec and 250–320 msec after stimulus onset. No group differences were found in response amplitude. On the other hand, the late vMMN amplitude correlated with the Hamilton rating scale for depression in the depressed group. However, although vMMN did not differ between the groups, they showed differential responses to the deviant and control stimulus (the same stimulus presented in an equiprobable control condition). This pattern of results does not provide a straightforward interpretation, but presumably there is a deficit in the processing of low-level visual features, and perhaps also in the detection of regularity violations, in depression.

In a study with depressed participants, Qiu et al. (2011) presented two black squares simultaneously for either 50 msec or 150 msec in duration. Both an increment and a decrement in duration were used in separate stimulus blocks as the deviant stimulus. Participants attended to changes in the size of a black cross in the center of the screen. The vMMN was calculated as a difference between responses to physically identical stimuli presented in the two stimulus blocks (i.e., responses to the 150-msec stimulus as deviant minus responses to 150-msec standard stimulus). In the 200–250 msec post stimulus analysis time window the mean amplitude of the differential response for the 150 msec duration stimulus was smaller in the depressed patients than in the controls. However, details of the analysis of standard and deviant responses were not reported, leaving it open whether the standard and deviant responses differed from one another in either of the groups.

Maekawa et al. (2013) used changes in spatial frequency of circular black-white windmill patterns as vMMN evoking stimuli in a group of BP patients and healthy controls. Participants were instructed to listen to a story presented through earphones, and also attend to visual stimuli and to press a button whenever a target stimulus appeared. It is worth noting, since the visual stimuli were also attended, that the study was not a typical vMMN study where visual stimuli are usually ignored. A six-vane and 24-vane stimuli were assigned as deviant and standard stimuli counterbalanced across the stimulus blocks. The vMMN at 200–350 msec latency range (mean amplitude values at the occipital electrodes) was right lateralized in the control group, but not in the BP group (Fig. 2). This finding suggests that the source of the activity is different between the groups. However, it was not reported whether the observed vMMN response was statistically significant in either of the groups. The response amplitude for the differential response at the 200–350 msec latency range correlated with the lithium dosage, but not with the symptoms.

Both depression and BP are also associated with abnormalities in emotion processing (for a review, see Phillips, Drevets, Rauch, & Lane, 2003). Visual MMN to changes in facial expressions has been reported several times in healthy participants (Astikainen, Cong, Ristaniemi, & Hietanen, 2013; Astikainen & Hietanen, 2009; Kimura, Kondo, Ohira, & Schröger, 2012; Li, Lu, Sun, Gao, & Zhao, 2012; Stefanics et al., 2012; Susac, Ilmoniemi, Pihko, & Supek, 2003; Zhao & Li, 2006). Because both depression and BP are associated with abnormalities in emotion processing, and since depression affects social cognition (Wolkenstein, Schönenberg, Schirm, & Hautzinger, 2011), vMMN seems to be a feasible tool to study altered emotion processing in this disorder. It is thus surprising that there is only one report on vMMN to facial expressions in depressed participants (Chang, Xu, Shi, Zhang, & Zhao, 2010).

Chang et al. (2010) presented schematic faces to depressed and control participants. Neutral standard faces were infrequently replaced by sad or happy faces, both drawn in red. Participants were instructed to count the target faces drawn in green. In two separate stimulus blocks, upright and inverted faces were presented. In the control group, emotional faces elicited larger responses relatively to neutral faces at posterior electrode sites. These differential responses were observed at the latencies of the N170 (early vMMN) and P250 (late vMMN) components. Both early and late vMMN were decreased in the depressive group indicating a deficit in automatic change detection in facial emotions in depression. Face inversion decreased the amplitude of vMMN in control group, but not in the patient group. This may indicate difference in high-level perceptual processing in depression and/or different connectivity in the face processing-related neural network (Matsuyoshi et al., 2015).

In addition to emotional visual stimuli, emotional auditory stimuli have been used to study information processing dysfunction in depression. Pang et al. (2014) found that sad prosodies in meaningless words did not elicit aMMN in comparison to neutral prosody in depression patients while no differences were found for happy or angry prosody in comparison to healthy controls. The aMMN did not correlate with depressive symptoms.

Summary of vMMN studies in mood disorders

Studies on aMMN have revealed alterations in processing of elementary sound features in mood disorders. These alterations are observed as decreased response amplitude (e.g., Kähkönen et al., 2007; Takei et al., 2009), delayed latency and different source location of the change detection-related activity (Takei et al., 2010). The previous studies in depressive participants have not found relationship between clinical

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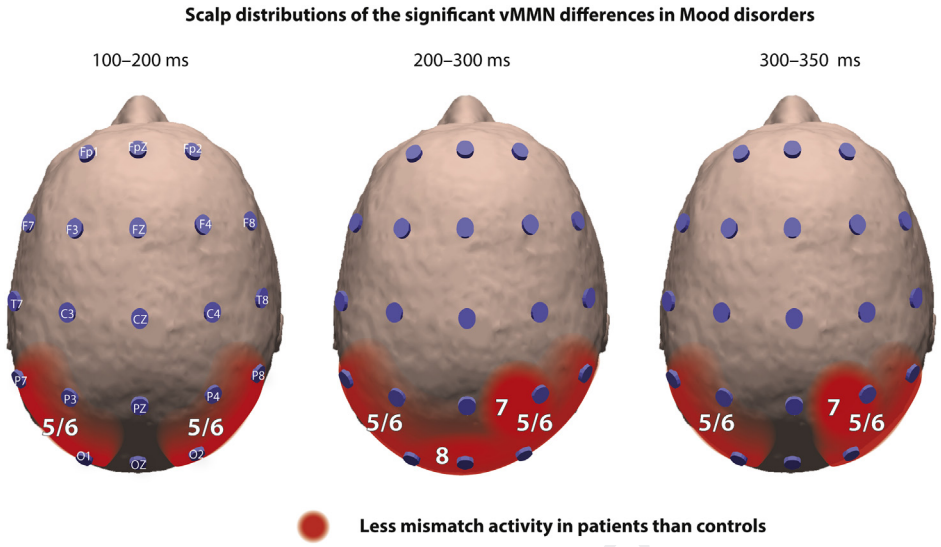

Fig. 2 – Scalp areas of a significant difference in the deviance-related activity between patients with mood disorders and controls. Numbers represent the following studies according to Table 1: 5 – Chang et al. (2010), 6 – Chang et al. (2011), 7 – Maekawa et al. (2013), and 8 – Qiu et al. (2011).

symptoms and aMMN (or aMMNm) amplitude or latency (Kähkönen et al., 2007; Takei et al., 2009).

One general aspect comes forth in all the vMMN studies related to mood disorders. Namely, standard and deviant stimulus responses were not compared directly (optimally by applying stimulus type factor in a multivariate statistical model). It is thus unclear whether the vMMN, i.e., differential response, was statistically significant. This methodological issue should be taken into account in future studies. In addition, future (vMMN) studies should explore whether processing deficit in the visual modality in depressed patients is related to visual feature processing, deviance detection, and/or emotional processing deficits.

Studies on vMMN in mood disorders could be useful in the future to disentangle different aspects of the cognitive dysfunction in these disorders. Especially studies using elementary visual features (e.g., orientation or color changes), abstract or rule-like changes (e.g., Kecskés-Kovács et al., 2013a) and perhaps also emotional changes like changes in facial expressions in same participant groups would be very informative. In a long run these vMMN studies can be applied for developing diagnostic tools.

2.3. *Substance abuse*

While the auditory MMN has been extensively used to study different forms of substance abuse (Näätänen et al., 2012), there are only four papers so far concerning substance abuse effects on the visual MMN. In auditory modality, tens of different substances have been investigated, starting from alcohol, caffeine, nicotine and opioids, ending in various drugs for treatment of psychiatric disorders (benzodiazepines, antipsychotic/neuroleptic drugs, GABA agonists/antagonists, adrenergic drugs, dopamine, serotonin, NMDA/glutamate), antihistamines and hormones/neuropeptides (Näätänen et al., 2012). In relation to vMMN, there are two studies using alcohol (He, Hu, Pakarinen, Li, & Zhou, 2014; Kenemans et al., 2010), one study on nicotine effects (Fisher et al., 2010), and one study investigating metamphetamine (MAP) effects on visual processing (Hosák, Kremláček, Kuba, Libiger, & Čížek, 2008). Two robust patterns emerge from these studies in accordance with previous studies on the enhancing or attenuating effects of those substances on visual information processing (see e.g., Newman, Speake, Armstrong, & Tiplady, 1997 for alcohol; Houlihan, Pritchard, & Robinson, 2001 for nicotine; and Kremláček, Hosák, Kuba, Libiger, & Čížek, 2008 for MAP). First, moderate acute dosage of alcohol diminishes the vMMN response to unattended and unpredicted stimuli. Second, both nicotine and MAP use enhance the vMMN response (for MAP, less than 5 years of use, see below for more details).

Even moderate doses of alcohol (blood-alcohol concentration – BAC about 0.05%) may have undesirable effects on human perception and performance, which is particularly evident and dangerous in road traffic (Heng, Hargarten, Layde, Craven, & Zhu, 2006). The narrowing of attention is one of the processes suggested to underlie the effect on human performance (e.g., Steele & Josephs, 1988). This is supported by studies showing reduced inhibition to visual stimuli, e.g., in a stop-signal task (Fillmore & Vogel-Sprott, 1999); when the subject is asked to perform more difficult dual-tasks (Fillmore & Van Selst, 2002); or when the central visual target stimulus is being flanked by response-incongruent stimuli (Eriksen flanker task, see Bartholow et al., 2003) (cf. Kenemans et al., 2010). Impairments of attention processing after alcohol consumption have been shown to be reflected in diminished amplitudes of ERP components N1, N2 (see Bijl, Bruin, Kenemans, Verbaten, & Böcker, 2005, for further references for alcohol-dependent subject groups) and P3 (e.g., Houlihan et al., 2001). The vMMN recordings may therefore yield insight into the source of the increased risk: the automatic attention-switching mechanism for visual change detection is dampened even by minor alcohol doses.

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Kenemans et al. (2010) used a visual oddball paradigm (9:1 standard to deviant ratio) with spatial frequency change as a peripheral deviant, while the subjects performed a visual discrimination task in the center of the visual field. They found that in young healthy subjects (university students) with BAC varying from 0.04 to 0.07 % (average 0.05% right before and 0.033% right after the ERP experiment), the vMMN amplitude for peripheral spatial frequency change was considerably reduced in most subjects. In contrast, the exogenous spatial-frequency dependent difference at 80 msec (Kenemans, Baas, Mangun, Lijffijt, & Verbaten, 2000) was unaffected by alcohol. Kenemans et al. (2010) concluded that even a moderate alcohol dosage considered legally acceptable in many countries reduced the sensitivity of the visual cortex to automatic detection of unexpected changes in the visual periphery, whereas alcohol effects are far less dramatic on low-level sensory processes. This is also supported by their behavioral results (as well as the behavioral results of the second vMMN study on alcohol effects by He et al., 2014) showing diminished reaction speed, but intact reaction accuracy in the central task, possibly reflecting stronger focus on the central task-relevant events while peripheral unexpected changes go unnoticed.

However, it is not yet clear, whether the abovementioned conclusions apply to all types of visual stimuli or if there is some feature-specificity to be considered, since another study investigating alcohol effects on the vMMN suggests that stimulus features also plays a role. He et al. (2014) used a new multi-feature vMMN paradigm (Qian et al., 2014; Shi, Wu, Sun, Dang, & Zhao, 2013) with three types of deviant stimuli – duration (60 or 100 msec deviants *vs* 20 msec standards), location (45° and 90° change in respect to standard stimulus' placement), and color (red and green deviants *vs* sea-green standards). The subjects were attending to the task that involved detecting changes of the size of a cross in the center of the screen, while the vMMN eliciting stimulus sequences were presented in locations surrounding the central stimulus (distance 2.8°). Twelve healthy subjects attended both alcohol consumption (dosage of 0.65 g/kg resulting in average BAC level 0.06 ± 0.005% before, and 0.048 ± 0.006% as measured after the experiment) and placebo conditions (separated by two weeks). The results showed that alcohol considerably decreased the vMMN amplitude for changes in peripheral stimulus location and duration whereas that for color change was not affected. The latter might be due to the physical stimulus properties – no reliable vMMN emerged to the green color deviant (compared to the sea-green standard), implying a relatively high level of change is required to elicit the color vMMN at first place (Czigler et al., 2002). An additional aspect (beside basic experimental design) that discriminated the two vMMN and alcohol studies was the usual amount of alcohol the participants consumed being considerably higher in Kenemans et al.'s study (15–20 standard drinks/week) than in He et al.'s study (3–12 standard portions/months) that may have led to shorter memory traces to begin with in the more drinking sample (e.g., Ahveninen et al., 1999). Otherwise, He et al. (2014) results are in line with the Kenemans et al. (2010) results, showing decreased the vMMN amplitude after acute alcohol consumption.

Previously, studies of alcohol effects on the aMMN have yielded an analogous data pattern as suggested by the vMMN results of Kenemans et al. (2010) and to some extent the results of He et al. (2014). Even minor doses of alcohol reduced the frontal aMMN subcomponent presumably reflecting attenuated involuntary attention-switching function, whereas the sensory-specific aMMN subcomponent (recorded as polarity reversal in mastoid recordings) was unaffected (Jääskeläinen, Pekkonen, Hirvonen, Sillanaukee, & Näätänen, 1996). More specifically the authors found that the attenuation of the aMMN amplitude even by a small amount of ethanol (0.55 g/kg) resulted from the decrement of the prefrontal rather than that of the supratemporal aMMN subcomponent. Kenemans et al. (2010) also replicated the experiment and the results of Jääskeläinen, Alho et al. (1996) and Jääskeläinen, Pekkonen, et al. (1996) showing that alcohol consumption (compared to placebo condition) reduced the amplitude of the frontal component of the aMMN in the 100–200 msec latency window. Consistent with this, a small amount of ethanol decreased the detrimental effect of the task-irrelevant auditory changes on performance accuracy in a visual forced-choice discrimination task, i.e., alcohol improved task performance (Jääskeläinen, Alho, et al., 1996).

Another relatively widely accepted legal substance people use for its effects on mood, arousal and cognition is nicotine. It is proposed that nicotine enhances cognitive performance in smokers and non-smokers probably due to sharpening of primary encoding of sensory and temporal stimuli presented outside the attentional focus (e.g., Fisher et al., 2010; Martin, Davalos, & Kisley, 2009). Nicotine is a cholinergic agonist that may also enhance the glutamatergic system and presumably through this alleviate some symptoms of schizophrenia (see also chapter 2.1 on schizophrenia). For example, it has been shown that nicotine may normalize duration (but not frequency) aMMN in schizophrenics (Dulude, Labelle, & Knott, 2010). This promising result is already a good justification for any attempts to test the nicotine effects on change detection in other modalities. There is a positive report from a study where acute nicotine effects on the vMMN were investigated by Fisher et al. (2010) in a randomized, double-blind, placebo controlled design in nonsmoking population (n = 27). The experimental paradigm had an intermodal design, where the vMMN-eliciting stimuli were vertical bars that differed in their length (long bars being standards, short ones deviants; standard to deviant ratio 3:1). The subjects' task was to attend to and respond to certain tones. Contrary to the authors' hypothesis, nicotine (administered as gum with 6 mg nicotine dosage that typically causes blood nicotine levels to rise 16–26 ng/ml in 25 min) did not affect response speed and accuracy measures of a concurrent auditory task. In contrast, the vMMN amplitude for visual deviant events in the center of the field of fixation was dramatically enhanced by nicotine. The authors proposed that nicotine enhances the vMMN amplitude by increasing the ability to encode and process information outside the attended (auditory) modality, such as visual deviant events, while protecting against any decrement in primary task performance.

VMMN has also been used for studying the effects of long-term methamphetamine misuse. MAP is a widely used amphetamine-based psycho-stimulant. Its effects on cognitive processing depend on doses and duration of abuse (Barr et al., 2006). Alertness, friendliness, "feeling high" and

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energetic, decreased food intake, and better subjective memory are among typical positive consequences of acute intoxication (Hart, Ward, Haney, Foltin, & Fischman, 2001). MAP abuse is related to damage in dopamine and serotonin systems with direct effects on cognition, most notably difficulties in suppressing irrelevant task information but also longer decision times or increased impulsivity (reviewed by Nordahl, Salo, & Leamon, 2003). Kremláček et al. (2008) tested MAP effects at the cortical level and reported slowing, attenuation, and reorganization of visual evoked potentials (VEPs) in response to pattern reversal of high spatial frequency checkerboards and visual motion in a group of 23 MAP users (with approximately 5 years of MAP abuse). In accordance with these effects, a vMMN study with low-contrast sinusoidal gratings moving fast (50°/sec) into opposite directions presented in the visual periphery for 200 msec also found that the vMMN amplitude for the motion direction was increased for short-time (less than 5 years) abusers, and decreased only for those who had abused MAP for more than 5 years (Hosák et al., 2008). It is unknown whether similar pattern occurs with aMMN as well, as we found no corresponding study with the auditory mismatch response, but we suggest that it is rather reasonable to look for it in a magnocellular task dealing with rapid temporal information. From a clinical point of view, as vMMN appears to reflect the severity of abuse it makes sense to examine it in addiction, in particular with respect to the possibility of monitoring the extent of sensory functional damage and recovery in cases of withdrawal,. It should be noted that beside automatic irregularity detection also other sensory mechanisms might be of interest, as it is evident from the study investigating VEPs (Kremláček et al. 2008) (Fig. 3).

Summary of vMMN studies in substance abuse

To conclude, vMMN seems to be promising for studying alcohol effects on rapid attention-switching and memory trace duration. VMMN results are in accordance with the studies using aMMN. An advantage of using vMMN rather than aMMN for studying alcohol effects might be its higher ecological validity, since in everyday situations (e.g., in traffic) people rely on and use visual input more than auditory input. One has to take into consideration, though, that the two existing vMMN studies report the dampening effects of acute alcohol consumption. However, similar changes in vMMN amplitude would be expected in case of chronic alcohol consumption as well, since studies using visual tasks on alcohol-dependent groups show diminished N1, N2 and P3 ERP components [see Bijl et al. (2005) for overview].

The neurobiological and genetic background of addiction and vulnerability has been thoroughly investigated. Using the vMMN component in the above conditions can provide information about the pharmacological mechanisms underpinning visual predictive processes and change detection.

2.4. *Neurodegenerative disorders (Alzheimer's disease – AD, mild cognitive impairment – MCI and spinocerebellar ataxia – SCA)*

AD is the most common form of dementia (Thies & Bleiler, 2013). It is an insidious, progressive neurodegenerative disorder accounting for 60% to 80% of cases. According to the World Health Organization there were an estimated 25 million people worldwide aged 65 years and older living with the disease in 2012. Characteristic brain pathology includes amyloid plaques, tau tangles, neuronal damage and death, while behavioral characteristics include inexorable decline in cognitive integrity, social interaction, self-care and quality of life. Although drugs cannot yet arrest disease progression, active management and behavioral intervention during the early stages of AD may confer some preservation of function, although short-lived, and improvement in quality of life (Thies & Bleiler, 2013). However, using current clinical test regimes, the very early stages of AD can be difficult to differentiate from

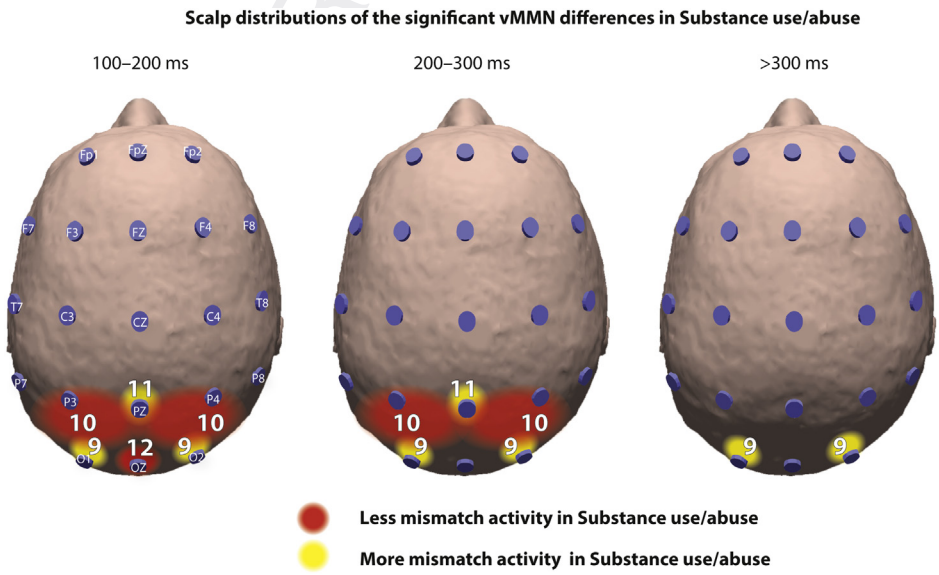

Fig. 3 – Scalp areas of a significant difference in the deviance-related activity in substance abuse compared to controls or control condition. Numbers represent the following studies according to Table 1: 9 – Fisher et al. (2010), 10 – He et al. (2014), 11 – Hosák et al. (2008) (note that vMMN decrease in >5 yr MAP use is not shown), and 12 – Kenemans et al. (2010).

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cognitively healthy aging and other factors influencing cognition. Consequently, research is increasingly focusing upon identifying changes in a wider range and level of brain functions (including fundamental levels of processing) than those relatively high-level processes measured at present.

One area of such research involves determining the functional integrity of visual information processing. Research increasingly reveals pathological and functional change in the visual cortex and disruption to a wide range of basic visual processes (see Stothart, Kazanina, Näätänen, Haworth, & Tales, 2014; Tales, Haworth, Wilcock, Newton, & Butler, 2008, for reviews). Evidence of pathological change in the visual extra-striate cortex (a region closely associated with the vMMN) indicates that abnormality in vMMN and its associated operations in AD should be considered a possibility.

Iijima, Osawa, Nageishi, Ushijima, and Iwata (1995), in an early study reported in a published abstract the preservation of the vMMN in older adults and in a group of patients with dementing illness of various etiologies. In a later study, Tales and Butler (2006) examined vMMN in cognitively healthy aging and AD. Participants were required to view a computer screen and to attend to a centrally placed small blue frame. Periodically, the area within this frame turned red (the target stimulus), to which a button press was required. A surrounding, larger blue frame defined an area where standard (single white bars) and deviant (double white bars) stimuli were presented. Target, standard and deviant stimuli appeared with a randomized inter-stimulus interval of 612–642 msec for a duration of 200 msec. The vMMN amplitude was measured over a 240–400 msec period after stimulus onset (Fig. 4).

For the young adults, a significant vMMN was evident in response to both the first and second blocks of trials, whereas the older adult group failed to demonstrate a significant vMMN in response to both blocks. However, although the AD group resembled the older group over the first block of trials, in that they exhibited no significant vMMN, they differed significantly from the older adults in the second block of trials by revealing a robust and significant vMMN (an effect resulting from an AD-related selective increase in the amplitude of the responses to deviants during the second set of trials). The aging-related reduction in vMMN was described by Tales and Butler (2006) as representative of a reduction in the efficiency of change detection, with the resurgence of the effect in AD possibly indicative of the known AD-related tendency for over-distractibility in response to novel or distracting stimuli and events within the environment. Thus unlike the efficient processing it represents in healthy young individuals, the significant vMMN in AD may reveal dysfunction at the level of automatic vision-related processing. However, the vMMN is not always found to be reduced in cognitively healthy aging (see the Section 2.6 in this review) and although this effect was repeated to some extent in a later study examining AD and mild cognitive impairment (MCI; a prodromal stage of AD for some individuals; Tales et al., 2008) the effects were dependent upon the epoch over which the vMMN was measured. Furthermore, Stothart et al. (2014), using the same stimulus paradigm, did not detect statistically significant difference between the vMMN amplitude in cognitively healthy aging and AD (although its duration was reduced in the AD group) and found evidence of late 'mismatch positivity' in individuals with MCI.

Clearly outcome variability is an issue and one that may relate to disease heterogeneity, together with inter-study variation in measurement parameters and analysis. Research on AD-specific effects of the vMMN has been further restricted by a lack of longitudinal analysis, which has precluded verification of disease etiology and resulted in a failure to determine within a given group for whom MCI represented the prodromal stage of AD. Other limiting factors include the difficulty of controlling the drug status of participants (both in relation to AD-specific intervention and medication for concurrent illnesses); the relatively small number of participants recruited and tested, the failure to take into account potential covariates such as cognitive reserve (education, intelligence), age, gender and disease stage, participant demographics, and treatment status.

Another disorder affecting visual areas and accompanied by abnormality in some aspects of visual information processing is SCA. This autosomal dominant neurodegenerative disorder is characterized by progressive movement abnormalities and cerebellar atrophy, with the common SCA genotype 2 (SCA2) typically associated with saccadic slowing, tremor and deterioration in attention, short-term memory and executive dysfunction (Kremláček et al., 2011). SCA-related abnormalities in visual processing lead to the prediction that an abnormal vMMN will also be evident in this disorder. Using a motion-related vMMN paradigm (in which the vMMN was calculated as an integral of the difference between the deviant minus the standard ERP within an interval 100–200 msec after stimulus onset), Kremláček et al. (2011) found generally preserved vMMN in SCA2, but also a positive correlation between the vMMN and age and age at SCA onset and a negative correlation between the vMMN and pathological load (CAG repeats – cytosine–adenine–guanine triplet coding protein ataxin-2). As highlighted by Kremláček et al. (2011), and similarly to studies of vMMN in AD, patient numbers were relatively small; a reflection of how difficult recruitment can be in such populations when rigorous inclusion and exclusion criteria are observed. However, despite these limitations, such studies show proof of concept in that such patients can be tested successfully using typical vMMN paradigms and that there is some evidence of potential abnormality in the vMMN in neurodegenerative disorders.

Summary in neurodegenerative disorders

Compared to the vMMN, the auditory MMN has been widely applied to the study of clinical populations, although once again, there are relatively few studies examining aMMN in neurodegenerative disorders such as AD and in other forms of dementia (see Näätänen et al., 2012 for a review and Riekkinen et al., 1997). Evidence in relation to AD again reveals a somewhat heterogeneous study outcome, which in part appears to reflect the choice of auditory features used to elicit the aMMN (see Näätänen et al., 2012 for a review) but note however that abnormal aMMN has also been reported in the behavioral variant of fronto-temporal dementia (Rowe, Hughes, & Nestor, 2009) and in dementia related to Parkinson's disease (Brønnick, Nordby, Larsen, & Aarsland, 2010).

While there is a relative paucity of studies, there is evidence to suggest that with further investigation and development, the vMMN may represent an important functional

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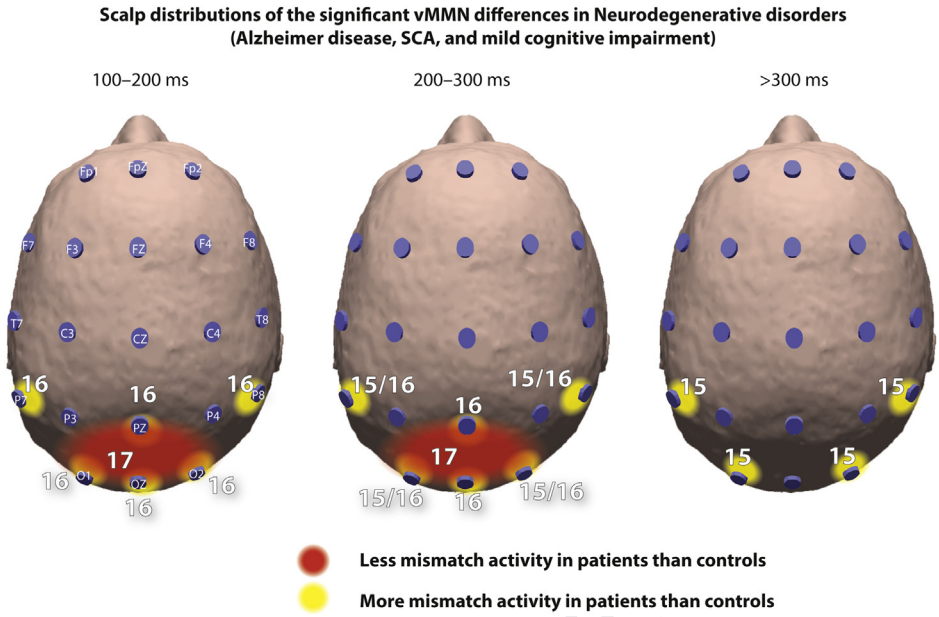

Fig. 4 – Scalp areas of a significant difference in the deviance-related activity between patients with neurodegenerative diseases and controls. Numbers represent the following studies according to Table 1: 15 – Tales and Butler (2006), 16 – Tales et al. (2008), and 17 – Stothart et al. (2014), studies without group differences are ignored. Note that patients in studies 14 and 15 showed the vMMN increase only in the second part of the examination.

characteristic of AD and related disorders. Although in the early studies by Tales and colleagues (see above), the relationship between a measure of cognitive integrity and the vMMN was not attempted, Stothart et al. (2014) found that the vMMN amplitude decreased with cognitive decline [as indexed by the mini-mental state examination (Folstein, Folstein, & McHugh, 1975)] score, a finding in agreement with several studies of auditory MMN (aMMN) in which reduced responses are observed across a wide range of pathologies associated with cognitive impairment. MMN therefore appears indicative of general cognitive integrity as well as reflecting early sensory processing (Näätänen et al., 2011).

It is clear that despite the substantial clinical and social importance of neurodegenerative disorders relatively few studies examining both visual and auditory MMN function have been performed. As well as improving participant numbers, future studies need to examine even earlier stages of AD and MCI, namely subjective cognitive decline (Jessen et al., 2014), together with other forms of dementia. Despite these limitations, such studies show proof of concept in that such patients can be tested successfully using typical vMMN paradigms and that there is some evidence of potential abnormality in the vMMN in neurodegenerative disorders which warrants further investigation. Only when more studies are performed can we work towards a consensus for what constitutes normative MMN data and what factors characterize specific pathological change.

2.5. *Developmental disorders*

Among the 33 vMMN studies[3] reviewed here six focused on developmental disorders, including autism spectrum disorders (ASD), dyslexia, and mental retardation. The ASD prevalence in school children is about 2% (Blumberg, Ph, & Bramlett, 2013) and etiology of the disease is not fully understood. In addition to impairment in cognitive and social interaction, sensory activation and habituation are also affected. The sensory impairment is frequently connected with a fascination in stimuli (e.g., visual motion) or fear of them (e.g., loud sound) and is related to a repeated movement pattern or stiffness in behavior. Since prevailing cognitive neuropsychological models cannot explain the aforementioned symptoms, hypotheses on sensory over- and/or hypo-arousal were developed. However, they do not have unequivocal experimental support yet (Rogers & Ozonoff, 2005), therefore vMMN studies might give contribute to the discussion.

The study of high-functioning ASD adults found an intact vMMN for the onset of a windmill pattern, however, the sensory response (P1) had a lower amplitude in standard and deviant stimuli, longer P300 latency and, interestingly, faster target detection compared to controls (Maekawa et al., 2011). The authors emphasized that they used non-social stimuli and interpreted their findings as an impairment of low-level processing and top-down modulation with preserved bottom-up attentional mechanism in the adult ASD patients. The protocol did not control the subject's attention that was oriented toward the deviant stimulus; therefore the measured vMMN might be confounded with attentional effects.

Another study employed socially relevant stimuli, such as happy or sad faces as deviant and neutral faces as standard

[3] Table 1. contains 35 experiments because different parts of two studies were used twice in our review: Horimoto et al. (2002) in Developmental disorders, and Aging and maturation, and Tales and Butler (2006) in Neurodegenerative disorders, and Aging and maturation.

stimuli to elicit the vMMN in a group of adults in whom Autism Spectrum Quotient (AQ) was measured (Gayle, Gal, & Kieffaber, 2012). Happy faces elicited vMMN within the 150–425 msec time interval at the occipito-parietal area. The vMMN showed a significant positive correlation with the AQ score: more negative vMMN amplitude was associated with lower AQ (higher quotient means more autistic symptoms). This finding was consistent with the authors' expectation that the vMMN might be a suitable indicator of affective reactivity in ASD. An absence of a control for physical differences between standard and deviant stimuli was limitation of the study.

A further study of adults with ASD (Cléry, Roux, et al., 2013) used two types of change in the shape of a circle as standard and deviant stimuli. The paradigm also included a novel, always different, circle deformation and the occasional disappearance of the fixation cross, to engage the subject's attention. Adults with ASD processed deviants differently compared to the control group. While controls showed vMMN in occipito-parietal (180–240 msec) and fronto-central areas (210–250 msec), the patients showed a late vMMP around 460 msec in occipito-parieto-temporal sites. Interestingly, the topography of the late vMMP was similar to that of the novelty P3. In addition patients with ASD also showed a significantly smaller negative component at around 160 msec for the standard and deviant stimuli, and a decrease in amplitude and a shift in latency of the later positive peak (240–310 msec). In contrast, the novel stimuli elicited quite similar ERP components in both groups including the novelty P3. Regarding behavioral results, there were no differences between groups in the accuracy or RT. This study indicates dissociation between the less effective automatic detection of deviancy and augmented processing of the attention orientation in patients with ASD. The authors conclude that their findings support a higher distractibility and a lower selectivity of the attention of patients with ASD reflected as patients' intolerance to a change.

Cléry, Andersson, et al. (2013) investigated 12 school age children with ASD and typically developing children with the same protocol as in their above study. The groups matched in chronological age showed a different pattern of deviance processing. While the controls had an early (280–340 msec) vMMP at fronto-central electrodes and a late vMMP at 450 msec at the occipito-parieto-temporal electrodes, children with ASD only showed the late vMMP that appeared significantly earlier than that of controls. The intergroup differences were restricted to the late vMMP only. The children with ASD also showed significantly prolonged early (obligatory) sensory responses and increased RT together with decreased accuracy of responses. The authors interpreted their findings reflecting an impaired sensitivity of ASD children to saliency and unselective processing of environmental changes.

An early study on visual mismatch responses compared autistic children to three control groups including typically developing children, children with dyslexia, and children with attention disorder (Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1994). The study used the pattern-onset of standard (rectangular shapes in the central part of a screen), deviant (180°-rotated standard) and novel (full screen letter "&") stimuli in two task conditions. The subjects fixated on the center of the screen in the passive condition, and counted the deviants in the active condition. At the time of the study, there was no agreement concerning the vMMN existence and as a visual alternative to the aMMN, a difference between the second positive and negative peaks (P2–N2) was used, and described as sensitive to the deviancy, independent of a task and without habituation (Kenemans, Verbaten, Melis, & Slangen, 1992). The authors found a significant interaction between groups (autistic *vs* the controls), task (active and passive) and stimulus (standard *vs* deviant or novel). The P2–N2 amplitudes of the autistic group were larger for the deviant stimuli in active condition compared to the passive condition; this result was not observed in control groups.

The afore-mentioned reports of adult patients do not yield a consistent picture of alterations of automatic visual deviance detection in the ASD. Whereas Maekawa et al. (2011) did not find any vMMN difference between patients and controls, Cléry et al. (2013) found that deviance processing is distinct in controls and the ASD patients, and in the latter group it resembles novelty detection. Gayle et al. (2012) described a relationship between autistic quotient and the deviance processing of socially relevant stimuli in healthy subjects. The only report of children with ASD (Cléry, Bonnet-Brilhault, et al., 2013) showed different characteristic of the visual deviance processing similarly to adults with ASD (Cléry, Andersson, et al., 2013) when compared to control group similarly to study of Kemner et al. (1994), which, in spite that did not recorded vMMN directly, explored effect of visual deviancy in autistic children.

Support for disturbed predictive processing also come from fMRI studies of RS. While for facial images RS was reduced in adults with ASD the RS for geometric shapes did not differ compared to controls (Ewbank et al., 2015a). RS for faces in patients with ASD was predicted from correlation analysis of RS and AQ in healthy controls (Ewbank et al., 2015b). Another prediction of a diminished RS for geometric shapes was not confirmed.

Considering the various symptoms of autism and inter-study methodological diversity, such a finding is not surprising. In spite of that, a dissociation between the sensory processing, the deviance detection, and the behavioral response was observed between controls and patients with ASD. Whereas studies in other disorders reported lower amplitudes or longer latencies of the early sensory response for standard or deviant stimuli, deviance detection was either similar (Maekawa et al., 2011) or even earlier (Cléry, Andersson, et al., 2013; Cléry, Bonnet-Brilhault, et al., 2013) in patients with ASD than that in controls. Such dissociation suggests 1) sensory impairment, and 2) disorganization of higher information processing in patients with ADS (Fig. 5).

Developmental dyslexia, a reading disability, has an estimated prevalence of 7 % (Peterson & Pennington, 2012). Although the etiology of dyslexia is not well understood, the current view supports an impairment of phonological processing (Norton, Beach, & Gabrieli, 2014), as well as sensory deficits (e.g., Kubová et al., 2015; Schulte-Körne & Bruder, 2010; Stefanics, Fosker, et al., 2011). Auditory MMN has been extensively used to investigate the development of the auditory and speech systems (Cheour et al., 1998; Háden, Németh, Török, & Winkler, 2015; Háden et al., 2009; Näätänen et al.,

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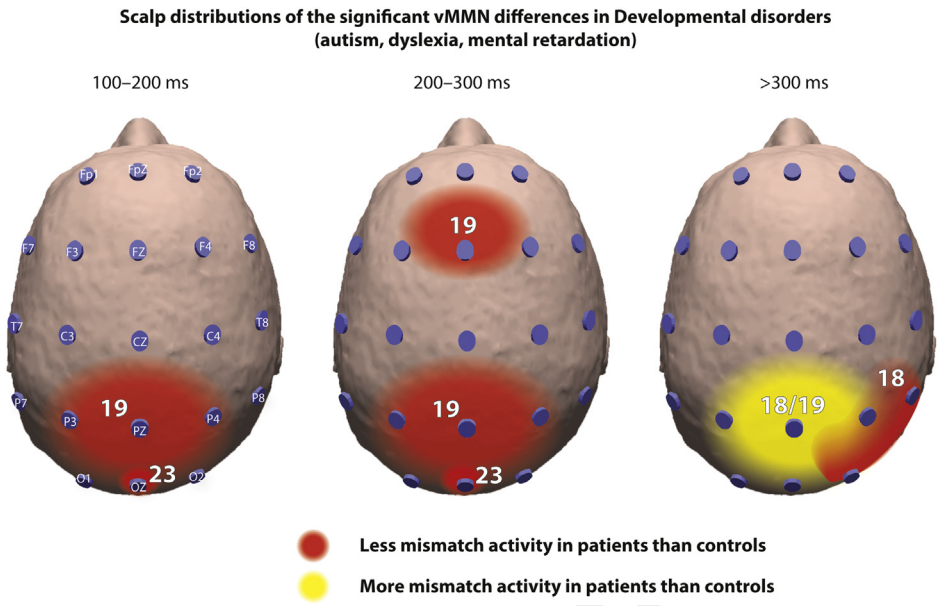

Fig. 5 – Scalp areas of a significant difference in the deviance-related activity between patients with developmental disorders and controls. The numbers correspond to studies in Table 1: 18 – Cléry, Bonnet-Brilhault, et al. (2013), 19 – Cléry, Andersson, et al. (2013), and 23 – Wang et al. (2010). Studies without intergroup difference are omitted.

1993; Stefanics et al., 2007, 2009), as well as their disorders (for a review, see Kujala & Näätänen, 2010). The phonological deficit hypothesis is also supported by aMMN studies (for a review, see Näätänen et al., 2012, 2014).

Besides the dominating phonological impairment hypothesis there are numerous studies indicating deficit of visual spatial attention (Vidyasagar & Pammer, 2010), temporal sampling (Pammer, 2013), audiovisual integration (Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Widmann, Schröger, Tervaniemi, Pakarinen, & Kujala, 2012) or an impairment of the magnocellular pathway and the dorsal stream (Stein, 2012). Interestingly, dyslexics exist also in logographic orthographies like Chinese, and there the etiology might be in favor of the visual disturbances. The only study of visual deviance detection was conducted among Mandarin Chinese readers and was oriented to discussion of the magnocellular deficit (Wang, Bi, Gao, & Wydell, 2010). The authors used a motion sequence of a low contrast and spatial frequency grating (a magnocellular stimulus) and a high contrast and spatial frequency grating (a control condition) and compared the vMMN between children with dyslexia, calendar age matched normal readers and reading level matched controls. An auditory task with postponed response was used to capture the attention. Visuo-spatial attention was oriented to the standard/deviant stimuli. The authors found a significant difference of the vMMN amplitude (150–250 msec) for the magnocellular condition between the dyslexia and both control groups at the Oz electrode. Such a difference was not present in the control condition (high contrast and spatial frequency). Together with behavioral results from a separate experiment assessing the choice RT to the same motion stimuli, the authors concluded that the magnocellular impairment is closely related to the orthographic processing impairment in the Chinese dyslectics. The aMMN for pitch deviance was also recorded in this study and no difference was found among the groups, which authors interpreted as a support for absence of the auditory deficit in Chinese dyslexics. The carefully prepared experiments in this study however suffered from an unclear selection of intervals for the vMMN evaluation.

Visual deviance detection was also evaluated among groups of children with idiopathic mental retardation (mean IQ = 66.7), adults, and control children (Horimoto et al., 2002). The stimuli were presented for 1 s in the screen center. A green square served as deviant, and a blue square as standard stimulus. The subjects fixated at the center and focused their attention to an auditory oddball task with tones presented between visual stimuli. Whereas for adult controls the vMMN was evoked at 250 msec at the Pz electrode, the vMMN in control children had a different morphology and was very difficult to identify in patients. Nevertheless, the authors described the dominant vMMN in the occipito-parietal region for control children and in the centro-parietal region for patients; however it is not clear whether the differences in the vMMN topography were statistically significant. Their experiment revealed a lower accuracy in the behavioral task and an unusually large early sensory response for the deviant stimulus in the patients. The authors concluded that children with mental retardation show an impairment of an early automatic change detection affecting the level of attention (Horimoto et al., 2002).

Summary of vMMN studies in developmental disorders

Current results support the use of the vMMN for examining sensory processing in developmental disorders. Specifically, the vMMN provides evidence of selective involvement of visual processing with intact auditory processing aMMN, in orthographic dyslexia (Wang et al., 2003). The vMMN showed differences in topography in children with ASD, while comparison between adults with ASD and control subjects failed

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to do so; a result possibly related to the varying use of shape or motion stimuli.

An inspiration for future vMMN studies is the aMMN study of Ceponiene et al. (2003) showing that the MMN was normal for non-social stimuli, and it was considerably reduced in amplitude for speech-sound stimuli in children with ASD. In the same vein, Kuhl, Coffey-Corina, Padden, and Dawson (2005) found that children with ASD showed a normal-size aMMN to change in non-speech sound stimuli but showed no aMMN in response to change in speech syllables. It seems that future study designs should benefit from using more socially oriented stimuli like faces and emotions, however they should also take into account demographic factors such as age, IQ, and ASQ as they exert an influence on the sensory results (Rogers & Ozonoff, 2005).

2.6. *Aging and maturation*

Newborns are not fully equipped with a perfect sensory system and cognitive abilities. Different abilities develop at different rates, probably due to diverse experience, rate of myelination and growth. For example, basic perceptual processes mature relatively quickly showing that visual acuity is at the adult level for 8 month old babies (Norcia & Tyler, 1985), and working memory in about the early twenties (Brockmole & Logie, 2013). Once at the peak, cognitive and sensory functioning will not last forever. Although growing older is not necessarily a clinical condition, a decrement in sensory (e.g., Cheng & Lin, 2012; Lindenberger & Baltes, 1994) and cognitive (Nyberg, Bäckman, Erngrund, Olofsson, & Nilsson, 1996; Park et al., 2002) processing may accompany an otherwise healthy aging (Shimamura, Berry, Mangels, Rusting, & Jurica, 1995). Both sensory discrimination and memory processes play a crucial role in automatic deviance detection indicated by MMN (Näätänen et al., 2007). Thus, MMN may be used to assess cognitive maturation or decline in aging.

There are four studies that assessed automatic change detection in the visual modality in otherwise healthy aged participants compared to young adults. Different stimuli and tasks have been used including shape discrimination (Iijima, Osawa, Nageishi, Ushijima, & Iwata, 1996; Stothart, Tales, & Kazanina, 2013; Tales, Troscianko, Wilcock, Newton, & Butler, 2002) and motion direction changes (Lorenzo-López et al., 2004). Lorenzo-López et al. (2004) used three age groups: young adults (32 ± 6 years), middle-aged (49 ± 4 years) and old (62 ± 3 years). The vMMN peak latency (measured in an oddball paradigm with 8:2 standard to deviant ratio) emerged between 145–165 msec in all age groups, with the only difference being that the older subjects showed vMMN in a smaller number of electrodes than young and middle-aged. A significant and progressive age-related reduction of the vMMN amplitude was reported between 165 and 205 msec. Tales et al. (2002) also showed a significant age-related decrease in the vMMN amplitude between young (mean age 30.5 years) and old (mean age 77, range 69–88 years) subjects, using an oddball paradigm (standard to deviant to target ratio 16:1:1; the experimental paradigm was the same as in Tales and Butler (2006) described in section 2.4 *Neurodegenerative disorders*). The group differences in amplitude occurred principally at posterior electrodes and the latency range observed was 250–400 msec. In the third study (Iijima et al., 1996) which used X and O stimuli (standard to deviant ratio 8:2), vMMN was measured from Fz, Cz and Pz electrodes, and showed similar latencies at all sites. The difference in amplitude or latency of the vMMN between young (20–29 years) and elderly (60–79 years)[4] group was not significant but surprisingly, elderly subjects tended to elicit vMMN more frequently than did young participants. The frequency of vMMN among subjects was not statistically evaluated, unfortunately; a later vMMP emerging at around 200 msec is visible in Fig. 1 of Iijima et al. (1996) and might show age group differences which were not reported. Differences between the two age groups emerged in more frequent N2b presence for the young subjects and delayed N2b for the elderly subjects showing that attentional processing was more sensitive to age. Similarly to Iijima et al., Stothart et al. (2013) did not find vMMN differences between young (20.8 ± 3.1 years) and old (76.8 ± 6.1 years) adults, as the vMMN was present in both age groups of subjects. They used the same experimental paradigm as Tales et al. (2002) (described in Section 2.4), who showed an age-related decrease in the vMMN amplitude. The authors argue that the differences may arise from not using the pre-defined temporal windows for assessing the vMMN mean amplitude; instead they adjusted their time windows according to the actual latencies (those being slightly earlier for the elderly subjects).

Even if no full-head montage of electrodes has been used, results of the above studies indicate that the main loci of the vMMN tend to emerge at O1, Oz, and O2 (Lorenzo-López et al., 2004; Stothart et al., 2013; Tales et al., 2002). These studies report a negative deflection peaking around 145–165 msec or later in averaged ERPs related to deviant detection. Different vMMN latencies may be related to the stimulus features. The control of attention may not have been an optimal in studies presenting the targets in a close vicinity of the standard/deviant stimuli (Stothart et al., 2013; Tales et al., 2002). As the ISIs used have been relatively short (1 sec or less), a contribution of conscious processing in the visual working memory has probably not been decisive as it has been shown that the retention depends on time (Baddeley, 2012). This is supported also by the absence of attention related components in the ERP waveforms.

Altogether, two out of four studies suggest that there is an age-related drop of the deviance-related potential, whereas other two report an intact vMMN. Since no aging effects on vMMN were present in the Iijima et al. (1996) and Stothart et al. (2013) studies, it still is unsettled whether healthy aging is necessarily accompanied by a decrement in the change detection mechanism in the visual modality. Stothart and his coworkers propose that instead there is an age-related compensatory neural response to impoverished sensory input in aging, reflected by reduced early sensory processing (decrease in P1 amplitude), but maintained object perception (increase in N1 amplitude) and change detection processes (intact vMMN amplitude). The decrease in the vMMN amplitude (Lorenzo-López et al., 2004; Tales et al., 2002) might,

[4] Iijima et al. (1996) reported different age ranges (22–29 and 62–72 years) in the full-text and in the abstract (20–29 and 60–79 years). Ranges from their abstract are used in this review.

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however, reflect a general decrease in cognitive performance as was reported for the aMMN (Gaeta, Friedman, Ritter, & Cheng, 2001; Kisley, Davalos, Engleman, Guinther, & Davis, 2005). This is also supported by the aforementioned studies on neurodegenerative disorders (Section 2.4) that do not focus on aging processes per se, while using elderly subjects as a control group for patients. Tales and Butler (2006) showed an age-related decline in the vMMN to shape discrimination between young (mean age 28, age range 20–43) and old (mean age 73 years and 2 months, age range 51–84) healthy adults in the 250–400 latency range, confirming their previous results (Tales et al., 2002). In the Tales et al. (2008) and Stothart et al. (2014) studies, only older adults (mean age 71.2 and 76, respectively) were used as the control group for the two patient groups. Similar experimental stimuli and paradigms were used as in Tales et al. (2002) and Tales and Butler (2006) studies, which makes the results of the control groups comparable to the two previous studies. Indeed, Tales et al. (2008) showed the absence of a significant vMMN response in the 250–400 and also in the 140–250 msec latency ranges, confirming their previous results. Stothart et al. (2014) showed a vMMN response in the 146–234 msec latency range, but no later vMMN and point out a rather large inter-individual variation in the vMMN response. Overall, the results of the elderly control groups of the three papers support the notion of an attenuated vMMN response in healthy aging.

In early development, opposite trends emerge than in the case of aging-related decline, but methodological diversity and possible developmental trajectories make comparing studies complicated. One of the earliest studies taking a developmental look at the vMMN (Tanaka, Okubo, Fuchigami, & Harada, 2001) used newborns (about 35–43 weeks of conceptional age). The authors showed that vMMN associated with depth perception measured with Ramachandran patterns (shadow-defined convex and concave interpretations) in a visual oddball paradigm (1:9 ratio of deviants and standards) was similar to frequency aMMN and the latency of both MMNs shortened with age. The observed decrease of about 100 msec of the MMN latency (measured from Pz) emerged between 36 and 37 weeks of conceptional age, being 519 ± 17 msec for 35 weeks old babies and 418 ± 58 msec for 37 week old babies (and staying rather stable from there on). The authors suggest that it is related to the cognitive status of newborns, specifically due to myelination and qualitative and quantitative changes in neurotransmitters in the brain. The study of Tanaka et al. logically led to a study with the same visual stimuli comparing subjects from 2 to 27 years (Tomio, Fuchigami, Fujita, Okubo, & Mugishima, 2012). The vMMN latency was again measured from Pz and showed a gradual decrease with an increasing age, being 394 ± 58 msec at the age of 2–3 and 273 ± 32 msec at 16 years, the latter reaching the same level as the vMMN latency for adults. Based on this study, it can be concluded that for depth perception, the perceptual system seems to work as effectively at about the age of 16 years as in adulthood (Fig. 6).

For color discrimination, the perceptual system of children seems to be comparable to that of the adults' one earlier – at about 10 years of normal development (Horimoto et al., 2002). Horimoto et al. compared normal school children (mean age 10, range 7–13 years) with adults (mean age 28.5 years), using color change as a deviant (1:4 ratio to standards). Both groups showed similar posterior vMMN peaking highest at Pz electrode in the observed latency range (180–400 msec): the vMMN amplitude was −4.8 ± 3.0 μV (at 250 ± 41 msec) in the adult group and only slightly (but not statistically significantly) higher in the children group. The vMMN in the children group had two peaks in the latency range of 180–400 msec. The authors conclude that the latency of the vMMN to color change reached the adult level in the 7–13 age-group and that the vMMN amplitudes were fairly similar.[5]

Cléry et al. (2012) used dynamic stimuli (deformation of a circle into an ellipse in one or another direction) in an oddball paradigm with healthy children (mean age 11.3, range 8–14 years) and adults (mean age 24, range 20–30 years). Both groups showed vMMN responses in occipito-parietal sites. The vMMN response in adults peaked at around 210 msec, while in children it seemed to have a longer duration between 150–350 msec with a broader peak, and was followed by a positive component (MMP450) around 450 msec. The same experimental paradigm was used in the Cléry, Andersson, et al., 2013 study, where children with ASD were compared to healthy control group (mean age 11.3, chronological age match to the ASD group). Similarly to Cléry et al. (2012), the control group showed a vMMN response peaking at around 330 msec in the occipito-parieto-temporal areas with a concurrent fronto-central positive component peaking at around 280 msec followed by a large positive wave peaking at around 450 msec. The authors suggest that this sequential change-detection process might be related to immature attentional abilities, that longer time is needed for children to process visual deviancy, and that slight variations in topographies reflect non-integrative processing of form and motion in children. Differently from Horimoto et al. (2002), the studies of Cléry et al. (2012) and Cléry, Andersson, et al. (2013) indicate that the vMMN to dynamic stimuli has not yet matured by the age of 11. The latter also applies to spatial frequency changes, shown by Cleary et al. (2013) comparing healthy children (mean age 10.4, range 8–12) and adults (mean age 26.6, range 18–42) with each other. The vMMN in children had a second peak at around 250 msec which was absent in the adult group, with a concurrent frontal positivity. The results support the idea that the change detection process is still under maturation in the 8–12 age group.

Summary in aging and maturation

Studies comparing the visual deviance detection between adults and children strongly support the modularity of such a system as the vMMN maturates differently for separate visual functions. This is consistent with different maturation of electrophysiological markers of visual sensory detection (Langrová, Kuba, Kremláček, Kubová, & Vít, 2006) and corresponds to the deviance detection in the auditory domain. A recent meta-analysis showed that deviance processing in the auditory modality is not a uniform process as it is more deteriorated in case of duration deviants than for frequency deviants and probably not changed for intensity deviants

[5] They also compared the normal children group with children that have mental retardation; those results are discussed in *Developmental disorders* section of this article.

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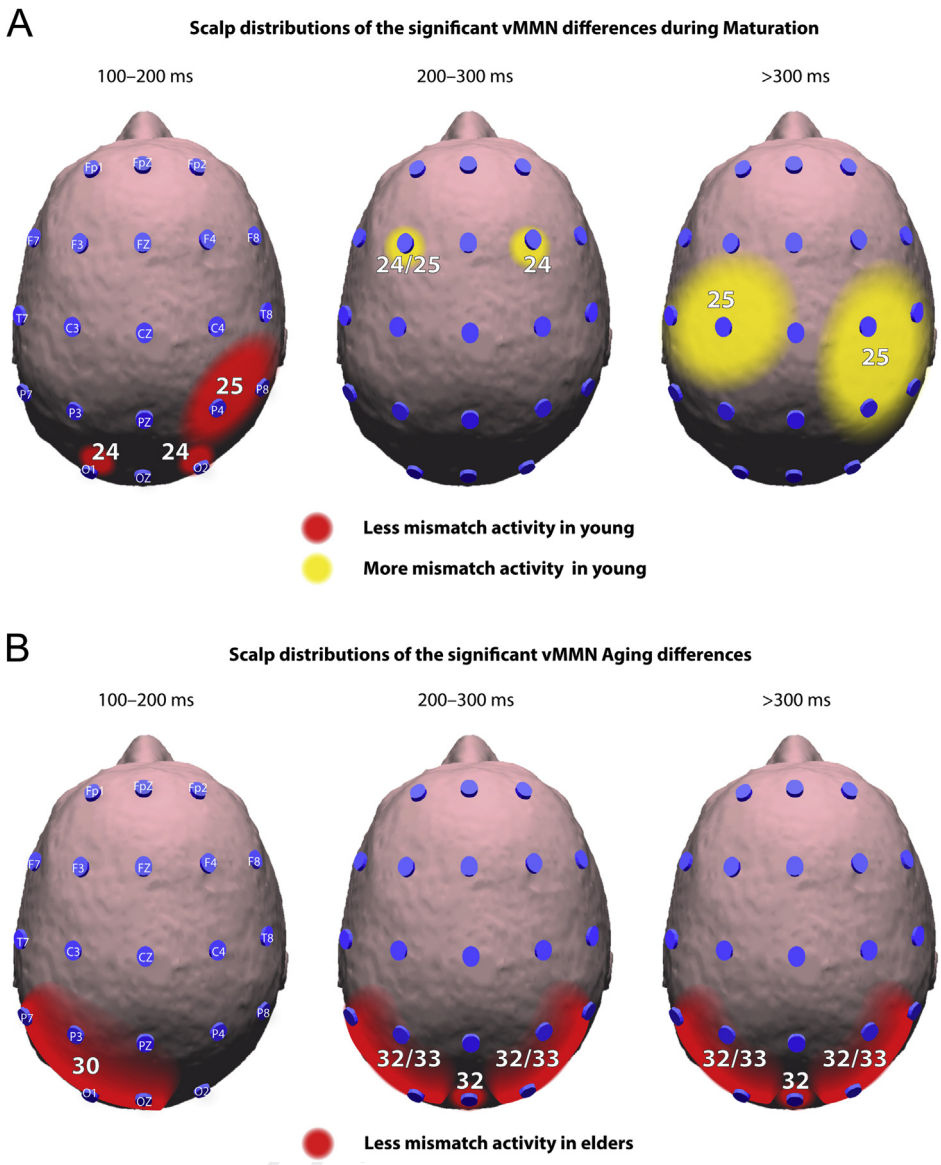

Fig. 6 – A) Scalp areas of a significant difference in the deviance-related activity between children and adult controls. Numbers represent the following studies according to Table 1: 24 – Cleary et al. (2013) and 25 – Cléry et al. (2012), studies without intergroup difference are ignored. B) Significant differences in the deviance-related activity between middle-age and elderly subject: 30 – Lorenzo-López et al. (2004), 32 – Tales et al. (2002), and 33 – Tales and Butler (2006).

(Cheng, Hsu, & Lin, 2013). The greater sensitivity of duration than frequency MMN to age and schizophrenia has also been reported (e.g., Todd et al., 2008). Thus, the vMMN may be used as a means to assess the opposing trends of cognitive maturation or aging.

There is a strong evidence of reduced amplitude and prolonged latency of the aMMN in healthy aging (for a review, see Näätänen et al., 2012). These age changes correlated to a decline of sensory memory maintenance, interestingly, its encoding was relatively preserved (Ruzzoli, Pirulli, Brignani, Maioli, & Miniussi, 2012). For this reason some studies using a short interstimulus interval (less than 2 sec) showed little effect of age on the aMMN (Cheng et al., 2013). Consequently the contradictory findings between young and elderly subject observed in vMMN might be caused/explained by the short interstimulus interval (below 1 sec) and therefore the age effect in the vMMN might be small and perturbable. Possible experiment addressing this issue should vary the interstimulus interval and relate it to the vMMN changes and to participants' age.

Since knowledge of the vMMN changes in healthy aging/maturation is crucial for potential search of biomarkers among various CNS disorders normative studies are of a substantial interest. As age changes of various electrophysiological components are distinct for separate visual subdomains (e.g., Kuba et al., 2012; Langrová et al., 2002), disproportional aging/maturation of the vMMN can be also expected. Research in this area will bring original findings.

As previously described in this review, no direct comparison between aMMN and vMMN have been performed and in

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future experiments evaluating the sensitivity/specificity of vMMN and aMMN should be balanced for saliency and attentional involvement. From the current perspective of vMMN research, there is not enough support for direct application of the vMMN in situations when healthy and pathological ageing/maturation should be separated for clinical purposes.

2.7. Miscellaneous

In this section we discuss clinically relevant vMMN studies which do not fit into the disorders grouped above. Bottari et al. (2014) compared vMMN between a group of subjects with early deafness and a hearing control group. The authors used motion stimuli in the near periphery of the visual field and allocated the subject's attention centrally by a simple detection task. The authors showed that the vMMN was evoked in the same interval (153–292 msec) in deaf and hearing subjects, but with a different distribution on the scalp. While in the control group, the vMMN dominated in parietal areas, whereas in the deaf group it was most prominent centrally. The authors suggested that visual deviance is processed by supramodal brain areas that, and in case of a deafferentation of auditory input in early childhood, they might shift from visual areas toward the auditory cortex, caused by cross-modal plasticity (Kujala, Alho, & Näätänen, 2000). Interestingly, the early ERP activity around 100 msec after stimulus onset was similar across groups.

Tang et al. (2013) examined vMMN in response to changes in facial expressions to study patients with panic disorder. According to previous results (H. Kessler, Roth, von Wietersheim, Deighton, & Traue, 2007), face processing and emotion detection is impaired in patients with panic disorder. Thus the vMMN for change of schematic facial expressions from positive to negative or vice versa was examined to reveal origins of the cognitive impairment. The authors found that the temporo-parietal and occipital vMMN in the 220–330 msec interval was significantly smaller in amplitude in patients compared to that of the controls. The authors suggested that the ability to automatically process facial expressions is impaired in these patients.

Moreover, Si et al. (2014), studying patients with hypertension, found that their vMMN to duration changes in stimuli randomly presented in both peripheral fields, was considerably attenuated in amplitude and delayed in peak latency compared with those of controls.

3. Discussion

As a result of the relatively narrow concept of the vMMN, the variability among experimental designs (see Fig. 7), and manifold diseases etiology thereby creating a wide spectrum of hypotheses, an individual summary for the specific clinical condition was presented at the end of each chapter. Here we summarize general views of the vMMN across all clinical conditions laying emphasis on observed effect size, correlations to other clinical parameters, and the spectrum of the experimental paradigms used. The discussion is closed by recommendations for further research.

3.1. Meta-analysis: Effect size and power in the reviewed vMMN studies

The amplitude of vMMN is usually in the range of a few microvolts, and signal to noise ratio of such a small response, as well as small sample sizes, might be an issue in some studies. To evaluate whether the reported effects have a relevant magnitude the effect size of clinical studies reviewed here was used. As the effect size was not always reported, we evaluated an equivalent Cohen's *d* effect (*eCd*) in this review. We derived the *eCd* using reported *p*, *F* or *r*-values and the group size. When a paired test was used in an original study then the *eCd* corresponds to Cohen's d effect measured between groups with an equal variability. The median of estimated *eCd*s was 0.97 (0.84; 1.17 – the first and third quartiles respectively), showing a large effect (Cohen, 1992). The largest *eCd*s per study with their respective 95% confidence intervals are plotted in Fig. 7. A considerable effect was a latency shift observed in three studies assessing the vMMN during maturation. This remarkable change in latency over maturation seems to be closely related to different projections of the vMMN on scalp in developmental and neurodegenerative disorders (Cléry, Andersson, et al., 2013; Cléry, Bonnet-Brilhault, et al., 2013; Horimoto et al., 2002), suggesting that the automatic deviance detection is likely accomplished by different neural networks.

Because of missing parameters for the *eCd* calculation, 6 studies were not included in the meta-analysis (Cléry, Andersson, et al., 2013; Cléry, Bonnet-Brilhault, et al., 2013; Iijima et al., 1995; Kremláček et al., 2011; Maekawa et al., 2011; Tales et al., 2008), therefore we evaluated 27 studies. Considering that 25 studies in Fig. 7 found a statistically significant group difference and usually there were 12 to 20 subjects per group then the large effect was a prerequisite for reaching statistical significance.

The issue of low statistical power in some studies is currently in the focus of several fields in neuroscience (Button et al., 2013). In our meta-analysis a corresponding power (*Pw*) was calculated from the *eCd*, respective group size and the first type error of 0.05. We found median power of 0.77 (0.60; 0.87 – first; third quartile). Button et al. (2013) meta-analysis of neuroscience field showed that median power of 730 primary studies was around 0.21, which is much lower compared to 0.77 obtained for the vMMN studies reviewed here.

Our meta-analysis of effect and power gives a reasonable expectation that observed vMMN changes have a solid statistical background. A possible limitation of such a conclusion is that that our meta-analysis was not corrected for publication bias, and several studies reviewed here might have suffered from circular inference (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009), e.g., due to a pre-selection of the intervals for statistical analysis based on visual inspection of the data. Such circular inference, also known as double dipping, might have led us to overestimate the observed effect. In future studies, it should also be taken into account that an initially reported effect is prone to extreme fluctuations, known as the Proteus phenomenon (Ioannidis & Trikalinos, 2005). In case of an original study where the effect was boosted by noise, overestimation might reduce reliability of the

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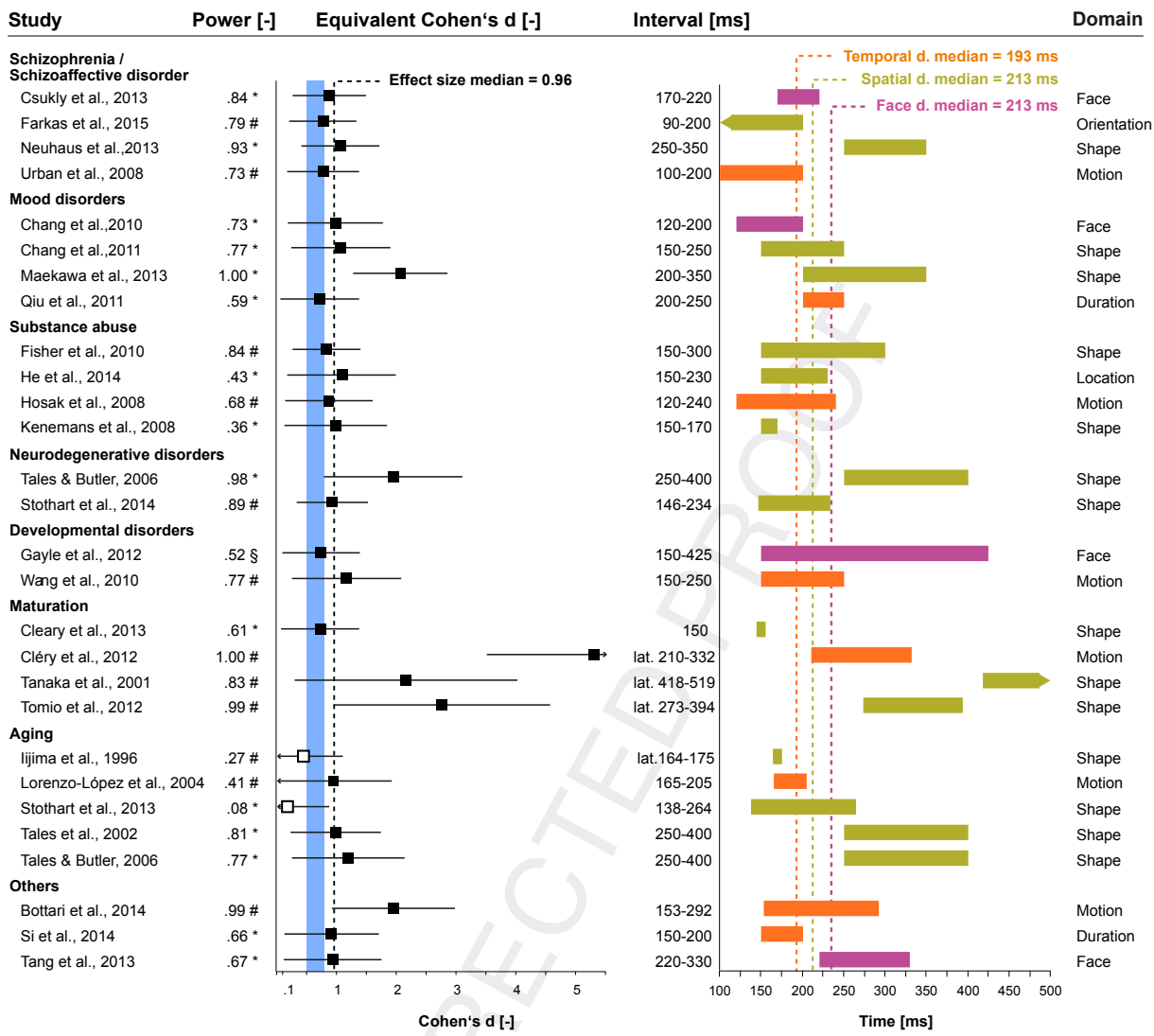

Fig. 7 – Equivalent effect size, study power, interval of difference and type of stimulation among selected studies (see *Effect size and power of the vMMN studies*). Forest plot in the left panel shows the estimate of equivalent Cohen's effect size (black squares for significant and opened squares for not significant observations), horizontal black lines represent 95 percentile intervals. Cohen's d was computed from the f value (marked as *), from the *p* value (#), or from correlation coefficient (§), as it is marked in the column *Power*. The power was calculated from the *eCd* and group size. The blue bar marks the interval of Cohen's d for a medium effect size (0.5–0.8). The dotted line delineates the *eCd* median. Forest plot in the right panel shows intervals of the vMMN difference between groups. The *Interval* column lists intervals in milliseconds for amplitude evaluation. In case when latency was assessed, the *lat* precedes the indicated interval of intergroup means. In the right side column *Domain* lists stimulus types used in the studies. The green bars mark a task with a spatial encoding of deviancy, and the orange ones represent the deviancy encoded by a temporal stimulus aspect.

effect size. Considering such possible tendencies, the size of the above *eCd*s should be judged with caution, and if possible, the lower ends of the effect estimates should be used. Since many of the studies reviewed have an explorative character we have to wait for replication studies to verify the observed effects.

3.2. *Correlations between vMMN and clinical indices*

Beside comparison of the vMMN between groups, the relationship between the vMMN characteristics (amplitude and/or latency) and clinical conditions is often assessed within a group to search for a trait or state marker or to address behavioral properties of the vMMN (Stefanics et al., 2014). Mostly a non-causal measure like Pearson or Spearman correlation is applied with a coefficient varying in interval from -1 to 1 based on the association of large and small values of the two analyzed parameters (Delorme, 2005).

The correlation analysis was conducted for 17 out of 33 reviewed studies and in 10 of them a significant relationship to various clinical parameters was reported (see Table 1). The vMMN latency was explored only in two developmental

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studies (Tanaka et al., 2001; Tomio et al., 2012), where the vMMN latency decreased with maturation. The remaining studies analyzed vMMN amplitude. Smaller visual mismatch responses were linked to more severe negative symptoms (Urban et al., 2008), and more positive vMM was associated with better facial emotion recognition skills (Csukly et al., 2013) in schizophrenia. In a study focusing on healthy adults more negative vMMN amplitude was associated with lower AQ (Gayle et al., 2012), however, in some subjects with a higher AQ the mismatch response was in the positive range. In general, the interpretation of such results is not straightforward.

Reports regarding the MMSE are equivocal and while Stothart et al. (2014) found that a lower MMSE corresponds to a less pronounced vMMN, such a relationship was not observed in a study of patients with dementia (Iijima et al., 1995) or hypertension (Si et al., 2014). Stothart et al. (2014) showed a positive relationship between the vMMN amplitude and the MMSE. They aggregated measures across three groups (elderly controls, patients with AD, and patients with MCI). For this particular case predominantly patients with the MCI had the positive amplitudes and therefore a compensatory mechanism, analogous to changes accompanying aging in vision (Stothart et al., 2013), might explain the vMMP. Furthermore, depression severity, assessed by the Hamilton Rating Scale of Depression, was found to be associated to the vMMN in the study by Chang et al. (2011) but not in the study by Qiu et al. (2011).

Regarding studies on substance abuse, while a longer methamphetamine abuse (Hosák et al., 2008) or a higher antipsychotic dose (Urban et al., 2008) corresponded to a lower vMMN amplitude, the level of alcohol consumption did not (Kenemans et al., 2010). However, these results should not be taken as a sign of inconsistency, because an acute intoxication was considered in case of the alcohol study and a long term effect of use/abuse was followed in the other two studies. Moreover the antipsychotics have diverse pharmacological effects on brain functions from sympathomimetic drugs like methamphetamine or alcohol.

3.3. *Stimulus features used for vMMN elicitation*

Various visual features (color, location, motion, shape, or facial expression) were used to establish regularity through stimulus repetition in the studies reviewed. In most studies an unexpected change in shape was used (Fig. 7) to violate the established regularity and elicit a mismatch response. The stimulus features used can be divided into two categories based on their presumed processing pathways. Specifically, we suggest that the ventral (what) and dorsal (where) visual stream (Ungerleider & Mishkin, 1982) might process spatial (shape, location, color, and face) and temporal (motion, duration) deviants, respectively. Figure 7 suggests that mismatch responses to deviants violating temporal regularities appeared earlier than for the spatial deviants. If we assume that representations of the diagnoses are balanced in both stimulus categories (see Fig. 7), it suggests that there might be an earlier deviance processing deficit for temporal stimuli compared to stimuli which violates a spatial regularity. This is not surprising, considering that the spatial stimuli might also combine several features (location, color, shape, or emotion) which might be attributes of complex objects that elicit mismatch responses at higher levels of the processing hierarchy with a corresponding impairment at longer latencies.

3.4. *Specificity to predictive processing*

A current hypothesis links the vMMN to predictive coding theories and suggests that the vMMN response represents a bottom-up perceptual prediction error signal as well as its ensuing top-down update process. Since the majority of the reviewed studies reported some kind of alteration of the deviance processing in various disorders, is it safe to say that an impairment of automatic predictive perceptual processes seem to be present in the very heterogeneous disorders reviewed here?

It was suggested that two underlying processes contribute to the vMMN, 1) response attenuation to repeated stimuli, and 2) the prediction error elicited by the unexpected event (Czigler, Sulykos, & Kecskés-Kovács, 2014). For assessment of the prediction error a subtraction of response to equiprobable control stimulus from the deviant response was proposed (Kimura, 2012). Among the reviewed studies, Chang et al. (2011) used this approach to compare patients with depression to a control group. Interestingly, the only difference they found between the groups was for the deviant minus the equiprobable stimuli. Such observation suggests that processes underlying stimulus repetition effects and prediction error generation might be dissociated and separately impaired in depression. Concerning other effects listed in this review, it is not possible to exclude that impairment of response attenuation might contribute to deficient vMMN in patients.

Impaired predictive processing might also manifest as a general sensory impairment. Such impairment would be present in a sensory evoked potential, sometimes called an obligatory response, recorded in a so-called one stimulus paradigm, e.g., in response to a repeating standard stimulus. Out of 33 reviewed studies 16 evaluated obligatory sensory components beside the vMMN. The sensory processing was disturbed in 13 of them (Bottari et al., 2014; Cleary, Donkers, Evans, & Belger, 2013; Cléry, Bonnet-Brilhault, et al., 2013; Cléry et al., 2012; Cléry, Roux, et al., 2013; Fisher et al., 2010; Iijima et al., 1996; Kremláček et al., 2011; Lorenzo-López et al., 2004; Maekawa et al., 2013, 2011; Stothart et al., 2014, 2013), whereas deficits only in components related to processing of deviants was observed in two studies only (Tales & Butler, 2006; Urban et al., 2008). The almost ubiquitous impairment of sensory stimulus processing in reviewed studies suggests that vMMN impairment is not necessarily the only candidate marker for impairments of perceptual processes.

3.5. *Limitations for clinical use*

It is often stated that using the vMMN does not require the subject's behavioral response for evaluating higher functions than sensory detection, e.g., sensory discrimination, as this ERP component is usually obtained in a passive paradigm. This, however, does not mean that patient's cooperation is not necessary. To control attention, a primary task is used which

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sometimes may be demanding, as patients have to be able to attend to, and perform, the primary task, and minimize movement during the EEG recording. Studying non-cooperative subjects can be more easily completed using auditory stimuli; however, visual stimuli might offer advantages which are not available in the auditory domain, such as testing predictive processing of information which can only be conveyed in the visual modality. The advantage of using vMMN to investigate specific hypotheses with appropriate control conditions for possible confounds arising from attentional modulation or specific sensory adaptation, comes at a cost of complex and time demanding protocols, which might impose limits on patient studies.

Auditory MMN studies suggest that some subjects, despite good stimulus discrimination and behavioral performance, do not show a reliable aMMN response. Bishop and Hardiman (2010) found that 82% of their healthy subjects (n = 17) showed a statistically reliable MMN component to pitch deviants. Thus, the interpretation of absence of a reliable vMMN response in a single subject might not always be straightforward also in vMMN studies, assuming that a reliable vMMN response in not observable in a subset of healthy subjects with otherwise good behavioral performance in stimulus discrimination.

4. Conclusions and directions for further research

We reviewed 33 studies where visual MMN has been used to investigate impairments of automatic perceptual processes in neuropsychiatric conditions. Our survey suggests that vMMN – similarly to auditory MMN – is a potentially useful tool for research in several clinical populations.

The deficits in vMMN in different disorders are not restricted to a certain time interval or scalp location. This is presumably due to the fact that different studies used different experimental stimulus sets, and brain areas generating the mismatch response to different stimuli might vary across studies. Furthermore, it seems plausible that there are multiple distinct physiological mechanisms that serve a common function: computing prediction errors and predictions. It is conceivable that these mechanisms might be altered differentially in specific disorders, or in different subgroups of the same disease, factors that might have contributed to the observed variability of vMMN findings across studies. We must point out that an optimal vMMN paradigm with control for all aspects of balanced design (see Technical notes at the end of the paper) has not been used frequently, and reproducibility, specificity, and sensitivity were not always estimated or addressed. Clinical studies using vMMN would benefit from standardized protocols as they allow for a broader replicability/reproducibility evaluation as well as multicenter studies.

Although there are now increasingly stratified treatments for psychiatric and neurological conditions, in most cases no clear indicators which treatment would be the best for a given individual patient are available. ERPs, including visual and auditory MMN, hold promise to serve as biomarkers for individually tailored treatments (Luck et al., 2011). Furthermore, they might be useful to evaluate new compounds and as diagnostic tools. However, the use of ERPs in guiding diagnostic or treatment decisions requires further basic research. There are open questions such as, which are the optimal paradigms, stimuli, and ERP components for each specific purpose. More advanced signal processing methods should be used to allow an optimal evaluation of an individual patient's ERP data and how these may change over time in relation to disease progression or remission/response to treatment. Since in many clinical conditions there is disturbed patients' attention it has to be stressed once again that the attention might modulate vMMN and therefore it should be controlled during examination. ERPs might prove useful also in dissecting heterogeneous disorders into more homogeneous subgroups. For example, a strong genetic component underlying depression might be observed as a distinct pattern of findings in ERPs compared to depression that has its roots in environmental stress. Unraveling these effects could allow a more accurate diagnosis and treatment guided by low-cost and non-invasive ERP recordings.

Future research would benefit from large-scale research projects comparing brain responses in different psychiatric and neurological disorders using similar experimental protocols. Also comparisons of brain responses in different stimulus conditions in the same group of participants are of interest. Future research should also test the predictive value of the vMMN for treatment outcome.

In clinical research both examination time and the patient's attention can be limited, therefore it is important to determine the most appropriate or potentially successful application of MMN. Regarding the optimal choice of a deviant feature to elicit the MMN in an oddball paradigm, the experimenter is not necessarily limited to using only one deviant stimulus type, as multi-feature paradigms that allow obtaining vMMN for several visual attributes in a short time are possible (Kreegipuu et al., 2013; Qian et al., 2014), some of which might prove more relevant in a particular population than the others. Another important choice is in which sensory modality should be the MMN investigated, e.g., visual and/or auditory. Although this review cannot give a clear answer as today there are only a few studies where both modalities have been tested, there are some situations where the disease directly influences the choice. While in schizophrenia the mean *eCD* vMMN was 0.86, meta-analysis of 32 aMMN studies showed comparably large Cohen's *d* effect of 0.99 (Umbricht & Krljes, 2005) and the impairment of the sensory processing seems to be general, only the vMMN and no aMMN was reduced in study of orthographic dyslexia (Wang et al., 2010). Furthermore, using aMMN is also not feasible in cases of severe auditory impairment, where, nevertheless, vMMN might be fruitful. For example, Bottari et al. (2014) used vMMN to assess plastic reorganization of the auditory cortex in early deafness and showed that cross-modally recruited auditory cortex participates in predictive processing of visual information.

Another field where vMMN might be potentially useful in clinical research is neuro-ophthalmology. Development of intraocular implants (Ahuja et al., 2011; Shepherd, Shivdasani, Nayagam, Williams, & Blamey, 2013) to artificially augment vision in blind people provides a unique opportunity for

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studying mechanisms of neural plasticity in the visual cortex. Furthermore, understanding plasticity could have major implications in the regenerative medicine of retinal diseases, such as age-related macular degeneration, retinitis pigmentosa, or other clinical conditions, e.g., long term visual deprivation, amblyopia, or stroke that involves cortical compensatory plasticity (Rosa et al., 2013). Since vMMN is relying on mechanisms of short-term plasticity, it might represent an important contribution to research in the above conditions.

VMMN opens new space for exploring automatic predictive processing of information with a substantial advantage over the aMMN where complex content have to be presented abruptly to elicit a brain response measurable with ERPs. A potential advantage of visual MMN over its auditory counterpart is that many particular visual stimulus "features" can be used to establish a statistical regularity which is not feasible using auditory stimuli. For example, although some emotional expressions have both visual and auditory components, the major channel for communicating emotions is visual via facial expressions. Thus, visual MMN might be well suited for studying the automatic perceptual component of social cognition (Astikainen & Hietanen, 2009; Stefanics et al., 2012) in disorders where it is impaired, such as in schizophrenia (Csukly et al., 2014; Kohler et al., 2003; Komlosi et al., 2013; Morris, Weickert, & Loughland, 2009). In general, VMMN might be a useful tool for studying deficits in predictive processing in cognitive domains where using visual rather than auditory stimuli is more adequate. Also, vMMN might be very useful when pathology is shown to potentially affect visual processing areas/or related neurotransmitters.

On the downside, using an appropriate visual distractor task to control attentional effects might be demanding for clinical populations. Controlling visual attention in MMN experiments is important to keep responses to unpredicted stimuli interpretable as prediction errors, free of potentially confounding effects of attention and task demands. Therefore using less demanding, but more entertaining, game-like tasks (Sulykos & Czigler, 2011; Kecskés-Kovács et al., 2013a) is important, and may counteract this possible drawback.

Visual MMN research, both basic and clinical, might substantially benefit from adopting the predictive coding perspective. Predictive coding provides a framework for theoretical models of perceptual inference, cognition, learning and decision making (Friston, 2005, 2010; den Ouden et al., 2012), and it might provide visual MMN research with a principled probabilistic approach to test neurophysiologically grounded hypotheses in clinical conditions (Adams, Stephan, Brown, Frith, & Friston, 2013; Corlett, Honey, Krystal, & Fletcher, 2011; Corlett et al., 2007; Friston et al., 2014; Stephan, Bach et al., 2016; Stephan et al., 2006; Stephan, Binder, et al., 2016; Stephan et al., 2009). Thus, it might help to understand better disease mechanisms and dissect heterogeneous clinical groups into well-defined subgroups to guide diagnosis, predict response to treatments or conversion to psychosis, or track disease progression. We believe that visual MMN, along to its auditory counterpart, might contribute to this process.

Although the potential for vMMN to serve as a specific clinical marker remains to be fully determined, this field is in its infancy, and though there is much debate regarding theoretical and methodological approach, the outcome of the studies described here highlight potentially clinically-relevant applications of vMMN and call for further research investment, addressing current limitations and proposing standardized protocols.

5. Technical notes

5.1. *MMN as differential activity*

The determination of an original condition (standard/deviant activation) from difference wave (MMN = Deviant – Standard) is an ill-posed problem, there being endless possibilities to generate the same differential curve (Fig. 8). Q6

Another important point to consider is using a proper control condition (for a review, see Stefanics et al., 2014). Studies using an oddball paradigm often record a so-called "reverse-block" where probabilities of the stimuli that served as frequent standard and rare deviant are reversed, which allows comparing responses to physically identical stimuli

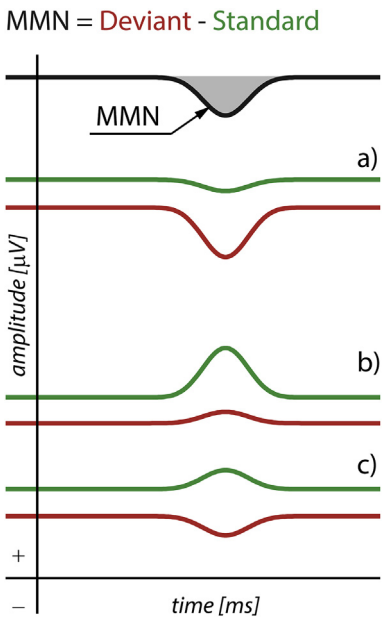

Fig. 8 – Different scenarios of deviant and standard responses that result in similar difference waves. Besides the situation (a), where the rare deviant stimulus elicits a larger negative potential than the repeated standard, there are also plausible scenarios, where (b) the standard stimulus elicits a more positive potential, which might correspond to potentiation in response to repeated stimuli described for example in migraine (de Tommaso et al., 2014), or where (c) responses with similar magnitude but with opposite polarity are evoked. For this reason it is advisable to include data both from the standard and deviant conditions in the statistical analysis and not only test the differential waveforms. Including stimulus types as a factor might reveal differences which would otherwise remain undetected.

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that were presented with different probability. An elegant method to control for effects both for physical features and probability is to use an equal probability control condition (Jacobsen & Schröger, 2001; Ruhnau, Herrmann, & Schröger, 2012; Schröger, 1997; Schröger & Wolff, 1996). For each disorder in the following sections we show scalp plots of group differences indicating altered deviance processing in a variety of disorders. However, as the above examples show these differences do not necessarily mean that patients have a smaller negative response to the deviant stimuli. Furthermore, the interpretation of differences in MMN between groups should be done cautiously as generating structures might differ between the groups which might result in different scalp potential topographies for patient and control groups.

5.2. *Limitation of the reported vMMN scalp distributions*

In this review we report electrode positions or scalp areas where differences between study groups in mismatch activity have been found. It should be emphasized that these locations do not necessary correspond to cortical sources of the MMN potential. The main reason is that distribution of scalp potentials depends on the reference electrode, and an electrically active source, which can project both to close as well as to distant parts of the scalp based on its spatial orientation (Nunez & Srinivasan, 2006). Source reconstruction might partially overcome these issues, however, the majority of the studies reviewed here did not perform source analysis.

It is worth to note that locations of the reported group differences could be affected by limited number of recording electrodes or by predetermined selection of the electrodes for statistical evaluation of the vMMN.

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